A 2,950-g female infant is born vaginally following an uncomplicated pregnancy, labor, and delivery. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Although mild tachypnea (respiratory rate, 60 to 70 breaths/min) was noted in the delivery room, she stayed with her mother and began breastfeeding. Because of difficulty with latching on the breast, she was re-evaluated and noted to have a respiratory rate of 84 breaths/min; no retractions or increased work of breathing was evident. Transcutaneous oxygen saturation was 85%. Arterial blood gases on room air showed: pH, 7.28; Paco2, 57 mm Hg; Pao2, 54 mm Hg; and base excess, -3 mEq/L. Nasal cannula oxygen is begun with Fio2 1.0 at 1 L/min. Portable chest radiography is obtained (Figs 1 and 2).

Of the following, the MOST likely diagnosis is:

1. bronchogenic cyst
2. congenital cystic adenomatoid malformation of the lung
3. diaphragmatic hernia
4. eventration of the diaphragm
5. unilateral primary pulmonary hypoplasia

You selected 3, the correct answer is 5.

Neonates who have unilateral primary pulmonary hypoplasia may be asymptomatic or present with severe respiratory failure. Primary pulmonary hypoplasia is an intrinsic developmental anomaly that affects right and left lungs with equal frequency. The condition usually is unilateral, but it may affect both lungs. Bilateral primary pulmonary hypoplasia is diagnosed only after excluding secondary causes such as oligohydramnios and skeletal or neuromuscular disorders, which may cause chest wall constraint. Congenital anomalies of the tracheobronchial tree, cardiovascular system, and vertebrae often accompany primary pulmonary hypoplasia. A small ipsilateral pulmonary artery and hypoplasia/absence of the ipsilateral bronchus frequently are present. Chest radiography shows variable degrees of pulmonary underdevelopment and, in the newborn, may show asymmetry of the thorax. In the anteroposterior chest radiograph obtained for the infant in the vignette, the right chest shows a relatively small right lung with rib space narrowing, mediastinal shift to the right, and relatively hyperlucent left lung. The lateral chest radiograph demonstrates a retrosternal density that is characteristic of primary pulmonary hypoplasia (small arrows); the tissue that causes this radiographic appearance is areolar and fatty tissue that replaces the hypoplastic lobes of the lung.

Bronchogenic cysts and other mediastinal structures may compress a bronchus and limit resorption of lung fluid after birth. Such bronchial obstruction results in a radiographic image of a unilateral, hazy, relatively large lung field with mediastinal shift away from the affected side. Bronchogenic cysts arise as abnormal buds from the developing tracheal diverticulum of the foregut prior to 16 weeks’ gestation. Most are near the right major bronchus and close to the midline. Bronchogenic cysts cause symptoms from bronchial obstruction as they enlarge in response to infection or, unusually, with expansion due to a direct connection to the trachea. Bronchogenic cysts do not present commonly in a neonate, but the diagnosis should be suspected when there is unilateral hyperexpansion of a single lung. Treatment is
Congenital cystic adenomatoid malformation results from an embryologic insult before 35 days of gestational age that alters development of terminal bronchiolar structures. Microscopic examination reveals glandular cells, cysts, and rarely, cartilage. The lesion usually is confined to a single lobe and may be large enough to cause mediastinal shift away from the affected side (versus toward the affected side in pulmonary hypoplasia). This is caused by failure of the pulmonary mesenchyme to develop normal bronchoalveolar structures, leaving hamartomatous and dysplastic changes mixed with normal lung. The three histologic patterns are: macrocystic lesion(s) greater than 2 cm in diameter lined with ciliated pseudostratified epithelium (mucus-secreting cells occur in about one third of these lesions) (Type 1); microcysts lined with ciliated pseudostratified epithelium (Type 2); and solid, bronchiolelike structures lined with cuboidal ciliated epithelium and separated by areas of nonciliated epithelium (Type 3). If the lesion enlarges, contralateral pulmonary hypoplasia may occur. In utero diagnosis is possible with ultrasonography, but variable degrees of regression or progression during fetal life make prognostication difficult. If hydrops arises, mortality risk is high. Prognosis is believed to be best for Type 1 and worst for Type 3 lesions. Radiographically, the affected lung appears as a density surrounded by radiolucent areas and compression of surrounding tissue. Computed tomography of the chest may be necessary for diagnosis. Surgical resection is indicated because of concern for neoplastic change in the affected lobe.

Congenital diaphragmatic hernia may be associated with asymmetric pulmonary hypoplasia, with the ipsilateral lung being most affected. Diaphragmatic hernia arises from failure of the pleuroperitoneal canal to close during the 8th week of gestation. The resultant diaphragmatic defect, most often in the foramen of Bochdalek, allows the intestine to move into the involved hemithorax as the midgut returns into the abdomen during the fetal period. The presence of intestine within the involved hemithorax is associated with lung hypoplasia; ipsilateral hypoplasia usually is more severe than contralateral hypoplasia. The left hemidiaphragm is involved in approximately 85% of cases, with bilateral involvement seen in 1%. Depending on the extent of pulmonary hypoplasia and the presence of other anomalies (about 30% of cases), symptoms may vary; presentation in the first hours after birth is associated with the highest risk for mortality. Chest radiographs classically demonstrate air-filled bowel loops on the side of the hernia and mediastinal shift away from the affected side. The contralateral lung may be hazy, long, and relatively small. Treatments vary with the severity of respiratory illness and may include mechanical ventilation, oxygen, inhaled nitric oxide, and extracorporeal membrane oxygenation; surgical repair is indicated after clinical stability has been achieved.

Eventration of the diaphragm is a congenital or acquired thinning or weakness of the diaphragm. Acquired lesions are due to paralysis following birth injury or surgery. Unless large, most eventrations are asymptomatic and discovered incidentally. Chest radiographs reveal elevation of the hemidiaphragm, usually anteriorly. If paradoxic movement of the diaphragm causes respiratory distress, plication may be indicated. Atelectasis may complicate the disease course.

References:


Swischuk, LE. Radiology of the Newborn and Young Infant. 2nd ed. Baltimore, Md: Williams and Wilkins; 1980

Content Specifications:

Recognize the radiographic features of congenital malformations of the lung, including congenital pulmonary lymphangiectasia, the cystic lung diseases, such as congenital lobar emphysema, cystic adenomatoid formation, and mediastinal tumors

Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress, such as diaphragmatic hernia, diaphragmatic paralysis, cord transection

Recognize the radiographic features of extrapulmonary causes of respiratory distress, including diaphragmatic hernia, diaphragmatic paralysis, and cord transection
You are evaluating the respiratory status of a 35-day-old male infant who requires mechanical ventilation. His estimated gestational age at birth was 24 weeks. He currently weighs 799 g. He has clinical and radiographic evidence of bronchopulmonary dysplasia. Physical examination reveals lability in oxygenation, coarse crackles throughout both lung fields, moderate retractions when agitated, good chest excursion, and an audible "oosh" during inspiration. His ventilator settings and respiratory mechanics on time-cycled, pressure-limited, synchronized mandatory ventilation mode with pressure support are found in the table:

The pressure-volume loop is shown in Figure 1.

Of the following, the ventilatory management step that is MOST likely to improve the respiratory status of this infant is to

1. decrease peak inspiratory pressure
2. increase positive end-expiratory pressure
3. insert a larger endotracheal tube
4. start high-frequency ventilation
5. switch to volume mode with pressure support

You selected 3, the correct answer is 3.

Minute ventilation normally is determined by multiplying tidal volume by the ventilatory rate during normal breathing and when using either time-cycled, pressure-limited, or volume modes of ventilation. Tidal volume is the amount of gas inspired during a single breath. The tidal volume generated passes into respiratory bronchioles, perfused alveoli, and pulmonary capillaries by convection (bulk flow) and molecular diffusion. A portion of the tidal volume also passes through the conducting airways (anatomic dead space) and into respiratory bronchioles and unperfused alveoli (alveolar dead space). Gas exchange does not take place in the total of these two dead spaces, which together constitute the physiologic dead space. Therefore, wasted ventilation occurs with each tidal volume breath and is represented by the ratio of dead space to tidal volume. With bronchopulmonary dysplasia, wasted ventilation may account for a relatively large proportion of the tidal volume generated, less effective minute ventilation during each breath, and respiratory acidosis.

During positive-pressure ventilation using time-cycled, pressure, or volume modes, the amount of wasted ventilation may be increased by the amount of gas that "leaks" or escapes around the endotracheal tube during inspiration. Uncuffed endotracheal tubes traditionally have been used for neonates to minimize local trauma to the trachea. Therefore, the optimal size is that which achieves minimal leak of inspired gas volume and minimal trauma to the trachea and larynx. The presence and amount of leak around an endotracheal tube during inspiration can be detected on physical examination by the presence of an audible inspiratory "oosh" or "wheeze," as reported for the infant in the vignette. The amount of the leak depends on numerous factors, including endotracheal tube size, airway resistance, gas flow, turbulence, inspiratory flow pattern, compliance, resistance, and patient effort.

Leaking of gas volume around the endotracheal tube can be confirmed and
measured by reviewing expiratory and inspiratory gas volumes and pressure-volume loops. Differences in inspiratory and expiratory volumes greater than 10% may indicate air flow leakage around the endotracheal tube. It should be noted, however, that measurement of inspiratory and expiratory gas volumes may be inaccurate, and falsely large differences may occur because of secretions, temperature fluctuation, humidity variation, calibration drift, inspiratory limb volume shifts, or computer integrator drift. If the accuracy of the data is questionable, removal of secretions, replacement of sensors, and recalibration may be necessary to confirm information before making ventilator adjustments. The vertical line in the pressure-volume loop depicted in Figure 2 is at the end of expiration, which indicates that the measured expiratory volume is lower than the inspiratory volume. This phenomenon occurs most commonly when gas volume is leaked around the endotracheal tube during inspiration. The length of the vertical line may be proportional to the volume of leak. If the inspiratory time is intentionally set to be longer than the expiratory time, it is possible that the inspiratory volume could intentionally be larger than the expiratory volume. However, this change is likely a short-term phenomenon because air trapping usually results in this setting. The intrathoracic pressure is raised and inspiratory volume limited when the peak pressure limits are reached before set or goal inspiratory volume is achieved. Therefore, if a leak around the endotracheal tube is audible, the presence and relative size of the leak may be confirmed and estimated by comparing expiratory and inspiratory volumes and pressure-volume loops as long as the clinician is confident that the measurement system is functioning properly.

Several measures to compensate for volume loss around endotracheal tubes have been introduced with different mechanical ventilators to improve tidal volume delivery. These measures include pressure-regulated volume-control ventilation, volume-guaranteed ventilation, and pressure-limited ventilation. Variable success has been achieved with these modalities due to previously discussed problems with volume measurements. The most appropriate strategy is to insert a larger endotracheal tube.

Decreasing peak inspiratory pressure reduces the driving, or compression, pressure (peak inspiratory pressure - positive end-expiratory pressure). Because the driving pressure is proportional to tidal volume, decreasing the peak inspiratory pressure decreases minute ventilation and worsens respiratory acidosis. Conversely, if the peak inspiratory pressure is increased, the driving pressure increases and, depending on the leak around the endotracheal tube, turbulence, compliance, resistance, and patient effort, may result in improved ventilation. However, altering peak inspiratory pressure is not a preferred strategy for addressing endotracheal tube gas leak.

Increasing the positive end-expiratory pressure reduces the driving pressure on the ventilator, resulting in worsened respiratory acidosis. In addition, increasing positive end-expiratory pressure increases mean airway pressure, which may increase lung overdistension. Although decreasing positive end-expiratory pressure increases the driving pressure and may enhance ventilation, it also lowers mean airway pressure and compromises oxygenation. Altering positive end-expiratory pressure will not help the infant in the vignette.

High-frequency ventilation in preterm infants who have bronchopulmonary dysplasia has not been demonstrated to improve ventilation. This lack of beneficial effect likely is due to high airway resistance and its negative effect on gas exchange.

Volume ventilation with pressure support has the potential to improve ventilation in a preterm infant who has bronchopulmonary dysplasia. However, no randomized trials have confirmed the efficacy of such a mode of ventilation. Migratory and shifting atelectasis commonly occurs in bronchopulmonary dysplasia and results in frequent compliance changes. Delivering a consistent tidal volume with volume-controlled ventilation may reduce the amount of atelectasis, frequent compliance changes, and episodes of oxygen desaturation. However, the leak around the
endotracheal tube reported for the infant in the vignette is substantial and likely to complicate gas delivery in both time-cycled, pressure-limited ventilation and volume-control ventilation.

References:


Content Specifications:

2343. Understand the pathogenesis and pathophysiology of bronchopulmonary dysplasia/chronic lung disease
1977. Understand the interpretation and limitations of methods for measuring lung mechanics
1577. Understand the determinants of gas exchange
A 2,200-g male infant is born vaginally following an uncomplicated pregnancy, labor, and delivery. Apgar scores were 3 and 8 at 1 and 5 minutes, respectively. Unlabored tachypnea (respiratory rate, 70 to 90 breaths/min) was noted in the delivery room, prompting admission of the infant to the neonatal intensive care unit. Transcutaneous oxygen saturation was 85%. Arterial blood gases on room air showed: pH, 7.30; Paco2, 51 mm Hg; Pao2, 54 mm Hg; and base excess, -3 mEq/L. Nasal cannula oxygen is begun with Fio2, 1.0 at 1 L/min. Portable chest radiography (Figs. 1 and 2) is obtained.

Of the following, the condition MOST associated with this diagnosis is

- biliary atresia
- cleft palate
- holoprosencephaly
- hydronephrosis
- tracheobronchial anomaly

You selected 4, the correct answer is 5.

Neonates who have primary unilateral pulmonary hypoplasia may remain asymptomatic or present with severe respiratory failure. Primary pulmonary hypoplasia affects both right and left lungs with equal frequency. The condition may affect both lungs, but it usually is unilateral. In contrast, secondary pulmonary hypoplasia is associated with restricted lung growth due to oligohydramnios or skeletal/neuromuscular disease. Congenital anomalies of the tracheobronchial tree, cardiovascular system, and vertebrae often accompany primary pulmonary hypoplasia. A small ipsilateral pulmonary artery and hypoplasia/absence of the ipsilateral bronchus frequently are present. Chest radiography shows variable degrees of pulmonary underdevelopment and, in the newborn, may show asymmetry of the thorax. Anteroposterior chest radiography of the infant in the vignette shows a relatively small right lung with rib space narrowing, mediastinal shift to the right, and relatively hyperlucent left lung. Lateral chest radiography reveals a retrosternal density that is characteristic of primary pulmonary hypoplasia (small arrows); the tissue that causes this radiographic appearance is areolar and fatty tissue that replaces the hypoplastic lobes of the lung.

Holoprosencephaly, hydronephrosis, biliary atresia, and cleft palate may be associated with syndromes that also affect lung development, but primary unilateral pulmonary hypoplasia infrequently is associated with anomalies of the brain, kidney, liver, or palate. Such anomalies may be seen if the unilateral pulmonary hypoplasia is part of a chromosomal disorder (eg, trisomy 13), a syndrome (eg, fetal phenytoin syndrome), or an association (eg, VATER association, CHARGE association).

References:

Aiton NR, Fox GF, Hannam S, Stern CMM, Milner AD. Lesson of the week: pulmonary hypoplasia presenting as persistent tachypnoea in the first few months of life. BMJ. 1996;312:1149-1150


Swischuk, LE. Radiology of the Newborn and Young Infant. 2nd ed. Baltimore, Md: Williams and Wilkins; 1980

Content Specification:

Recognize the clinical features of congenital malformations of the lung, including congenital pulmonary lymphangiectasia, the cystic lung diseases, such as congenital lobar emphysema, cystic adenomatoid formation, and mediastinal tumors.
An 8-week-old child is being seen for a health supervision visit by his pediatrician. His mother reports that he is wheezing and having increasing difficulty while feeding. Physical examination reveals a raised, erythematous birthmark on the chest and biphasic stridor on auscultation. The pediatrician calls a neonatologist to discuss the case.

Of the following, the MOST likely finding would be

1. a prolapsing epiglottis on nasopharyngoscopy
2. a unilateral subglottic mass on fluoroscopy
3. left mainstem bronchomalacia on bronchoscopy
4. obstructing adenoids on lateral neck radiography
5. unilateral air trapping on chest radiography

You selected 2, the correct answer is 2.

Biphasic stridor is produced by rapid turbulent flow of air through a narrowed segment of the airway. Stridor that is biphasic suggests an anatomic location at the glottic or subglottic level. Inspiratory stridor typically is produced by an obstructive lesion above the vocal cords, and expiratory stridor indicates an intrathoracic site of obstruction.

Subglottic hemangioma is a benign vascular malformation that typically enlarges over the first few months of life. Patients often are asymptomatic or minimally symptomatic at birth, then develop biphasic stridor, as reported for the infant in the vignette. The natural history is gradual enlargement until 1 year of age followed by slow involution to complete resolution. Fluoroscopy most commonly reveals a unilateral subglottic mass. Fifty percent of affected children have an associated cutaneous hemangioma, such as the erythematous birthmark described in the vignette. Definitive diagnosis is made by microlaryngoscopy in the operating room. Carbon dioxide laser excision, systemic or intralesional steroids, and tracheotomy have been used for treatment.

Inspiratory stridor in infancy most commonly is caused by laryngomalacia or prolapse of the supraglottic structures into the glottic introitus upon inspiration. Laryngomalacia can be diagnosed by nasopharyngoscopy. It usually is benign and resolves without intervention in 90% of patients by 1-1/2 years.

Vocal cord paralysis is another common cause of inspiratory stridor that may have a mild expiratory component. Airway fluoroscopy or nasopharyngoscopy is diagnostic.

Expiratory stridor most commonly is caused by tracheomalacia. This may present at birth and improve slowly over time; intervention rarely is required. Vascular compression may occur from an aberrant innominate artery that can compress the anterior trachea. Vascular rings (eg, double aortic arch) can compress both the trachea and esophagus. Retroesophageal subclavian compression typically causes dysphagia, but it also may result in respiratory symptoms. A diagnosis of tracheal anomaly and vascular lesion may be suggested by findings on chest radiography or airway fluoroscopy. Barium swallow demonstrates a typical indentation from posterior vascular compression in patients who have vascular rings or an aberrant subclavian artery, but it will not identify anterior compression from an aberrant...
innominate artery. Flexible or rigid bronchoscopy can be used to confirm the degree of compression of the trachea from any cause. In patients who have suspected vascular airway compression, magnetic resonance imaging or computed tomography is used to define abnormal vascular anatomy.

Obstructing adenoids can cause upper airway obstruction. Patients typically snore without accompanying stridor when tonsils and adenoids are hypertrophied. Although lateral neck radiography is a helpful diagnostic test for children who have adenoid hypertrophy, the clinical findings described in the vignette do not make this diagnosis likely.

Congenital subglottic stenosis may be either membranous or cartilaginous. Stridor is typically present at birth and may worsen slightly over time. The diagnosis may be made by plain radiography, fluoroscopy, or endoscopy. Microlaryngoscopy in the operating room is the most accurate diagnostic method. The anomaly usually is symmetric and bilateral or circumferential.

Unilateral air trapping on chest radiography is suggestive of unilateral compression or obstruction of the bronchus. In older infants, the most common cause is a foreign body. Bronchomalacia or other bronchial anomalies are diagnosed most commonly by bronchoscopy, but clinical findings would include expiratory wheezing rather than biphasic stridor.

References:
Holinger LD. Etiology of stridor in the neonate, infant and child. Ann Otol Laryngol. 1980;89:397-400

Content specification(s):
Know the various causes of stridor in the newborn
You are called to evaluate a 7-hour-old male infant, whose estimated gestational age is 26 weeks. He is receiving mechanical ventilation and has had an abrupt decrease in oxygen saturation (Sao2 of 68%). Prior to this event, he had been weaned to a peak inspiratory pressure of 17 cm H2O, positive end-expiratory pressure of 6 cm H2O, ventilator rate of 26 breaths/min, and Fio2 of 0.38 in the time-cycled, pressure-limited mode on the ventilator. After ventilating with a manual resuscitator through the endotracheal tube, the oxygen saturation rises to 88%. An arterial blood gas reveals: pH of 7.09, Paco2 of 82 torr, Pao2 of 57 torr, and base excess of -4 mEq/L. A chest radiograph shows gross hyperexpansion, with coarse linear and cystlike radiolucencies throughout the lung.

Of the following, the intervention that is MOST likely to improve the pulmonary function of this infant is:

1. extracorporeal membrane oxygenation
2. high-frequency jet ventilation
3. prone positioning
4. systemic corticosteroids
5. thoracentesis

You selected 2, the correct answer is 2.

Pulmonary interstitial emphysema is one of several air-block syndromes that complicate respiratory distress syndrome (RDS) in preterm infants; others include pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema, and intravascular air. All of these syndromes begin with some degree of pulmonary interstitial emphysema. High intra-alveolar pressure causes rupture of air into the perivascular sheath that surrounds intra-alveolar capillaries and into the lymphatic tree within the interstitial tissues of the lung. The presence of air in these spaces, rather than in alveolar sacculles and the tracheobronchial tree, is pulmonary interstitial emphysema. Of note, interstitial air usually does not collect in peribronchial spaces. Air then may dissect along the perivascular sheath toward the hilum of the lung where blebs collect at the reflection of the visceral pleura onto the parietal pleura. Air also may dissect to form blebs under the subpleural surface of the lung. These blebs of air may be reabsorbed or dissect into the pleural space to cause pneumothorax. If the blebs of air at the hilum are large or drain into the mediastinum, pneumomediastinum results. Air also may dissect into the peritoneal space (pneumoperitoneum) along the pulmonary ligament, intravascular space (air emboli), and subcutaneous spaces; these latter air-block syndromes usually occur with severe respiratory failure that requires high levels of mechanical ventilation support.

Microscopic sections of lungs with pulmonary interstitial emphysema show an irregular pattern of lymphatic distention, with air and arterioles enveloped by air. Radiographs show linear and cystlike radiolucencies of variable size. The linear densities extend from the hilum to the periphery of the lung and have few branches; they must be differentiated from air bronchograms seen with RDS, which most often are located near the hilum of the lung and have many branches. The cystlike radiolucencies range from 1.0 to 4.0 mm in diameter and may be oval or lobulated; they may cause the chest radiograph to look “spongy”. Air trapped within the interstitial spaces of the lung increases gas volume, which also causes the lung...
fields to appear hyperexpanded. The physiologic consequences of pulmonary interstitial emphysema include loss of compliance, increased airway resistance, ventilation-perfusion mismatching, increased pulmonary vascular resistance, decreased venous return to the heart, and reduced cardiac output. Hypercarbia, hypoxemia, hypotension, and increased cerebral venous pressure then may occur.

High-frequency jet ventilation is the intervention most likely to improve respiratory failure in the infant described in the vignette. High-frequency jet ventilation improves respiratory failure in preterm infants after air-leak syndromes such as pulmonary interstitial emphysema and pneumothorax have developed. Ventilation pressures were reduced and pulmonary interstitial emphysema resolved more rapidly in a randomized, multicenter trial of high-frequency jet ventilation after pulmonary interstitial pressure developed. High-frequency jet ventilation is not recommended for primary treatment of RDS because it may be associated with periventricular leukomalacia. High-frequency oscillatory ventilation is considered an alternative to high-frequency jet ventilation in preterm infants who have pulmonary interstitial emphysema.

Extracorporeal membrane oxygenation is the prolonged use of cardiopulmonary bypass in neonates who have respiratory or cardiac failure and are failing to respond to maximal medical therapies. Because the risk of cerebral hemorrhage in infants who weigh less than 2 kg or are younger than 34 weeks' gestation at birth is high due to use of systemic heparin during cardiopulmonary bypass, extremely low-birthweight infants are not candidates for this intervention.

Prone positioning has not been proven to improve the outcome of extremely low-birthweight infants who have pulmonary interstitial emphysema. Many clinicians position the infant with the involved lung down when unilateral pulmonary interstitial emphysema is present. Alternatively, unilateral mainstem intubation has been used in case studies for infants who have unilateral pulmonary interstitial emphysema.

The use of systemic corticosteroids in extremely preterm infants who have respiratory failure generally is reserved for those who have severe chronic lung disease, hypotension unresponsive to vasopressors, or suspected vocal cord or tracheal edema at time of extubation or for infants enrolled in randomized, controlled trials. Although dexamethasone may reduce the risk of death or bronchopulmonary dysplasia when administered early in the course of respiratory failure, the risk of adverse effects is high. The high risk for intestinal perforation, cerebral palsy, growth failure, hypertension, hyperglycemia, and adrenal suppression should be considered carefully when deciding to use systemic corticosteroids during the first postnatal weeks and months in preterm infants who have respiratory failure.

Thoracentesis to decompress pulmonary interstitial emphysema without a large pneumothorax is unlikely to improve the outcome for the infant in the vignette. In fact, thoracentesis may cause pneumothorax and acute deterioration in cardiopulmonary status.

References:


Content Specifications:
Understand the indications for and techniques of high-frequency ventilation
Understand the pathophysiology of air leaks
Recognize the radiographic features of air leaks
Understand how to prevent and manage air leaks
Coarse linear and cystlike radiolucencies throughout the lung
A newborn whose estimated gestational age is 42 weeks is stained with meconium. Tracheal intubation reveals meconium in the hypopharynx as well as below the vocal cords. The infant has respiratory distress. A chest radiograph is obtained.

Of the following, the MOST likely radiographic finding is:

1. coarse infiltrates
2. decreased lung volumes
3. mediastinal shift
4. pleural effusion
5. reticulogranular pattern

You selected 5, the correct answer is 1.

The postterm infant described in the vignette most likely has meconium aspiration, and chest radiography in this condition typically shows coarse, diffuse, bilateral infiltrates with irregular densities of consolidation. These infiltrates persist beyond 48 hours of postnatal age, in contrast to the infiltrates associated with retained lung fluid, which usually resolve within 24 to 48 hours. Chest radiography also may reveal cardiomegaly, possibly as a consequence of perinatal asphyxia.

Hyperinflation of the chest is more common than decreased lung volumes in meconium aspiration. Hyperinflation on chest radiography is characterized by flattening of the diaphragm. A lateral view reveals an increased anterior-posterior diameter; a barrel-shaped chest is evident on physical examination. Hyperinflation of the chest in meconium aspiration is attributed to air trapping from ball-valve obstruction of the airways by meconium plugs.

Mediastinal shift is uncommon in meconium aspiration unless the clinical course is complicated by a pneumothorax. Pleural effusion also is uncommon in meconium aspiration unless the clinical course is complicated by pneumonia or fluid overload. Neonatal sepsis and pneumonia should be suspected if a pleural effusion is present. A small pleural effusion on chest radiography is characterized radiographically by depression of the diaphragm on the affected side and displacement of the mediastinum. Typical conditions associated with a large pleural effusion include chylothorax, congenital pulmonary lymphangiectasia, and hydrops fetalis.

A diffuse reticulogranular pattern in both lung fields with superimposed air bronchograms is characteristic of hyaline membrane disease. The granular pattern is caused primarily by alveolar atelectasis, although there may be some component of pulmonary edema. The prominent air bronchograms represent aerated bronchioli superimposed on a background of nonaerated alveoli. Heart size is typically normal. However, cardiomegaly may be present as a consequence of birth asphyxia, in infants of diabetic mothers, or because of cardiac failure resulting from a symptomatic patent ductus arteriosus.

References:
Martin RJ, Fanaroff AA. The respiratory distress syndrome and its management. In: Fanaroff AA, Martin RJ, eds. Neonatal-Perinatal Medicine: Diseases of the Fetus and


Content Specification(s):

Recognize the clinical, laboratory, radiographic, and pathologic features of meconium aspiration syndrome.
A pediatrician calls you regarding a 1-month-old boy who has had inspiratory stridor since birth. The stridor is associated with retractions when the infant becomes agitated. Physical examination reveals a weight of 3.4 kg (10th percentile), no expiratory stridor, and weak cry.

Of the following, the MOST likely cause of the stridor in this infant is

- bilateral paralysis of the vocal cords
- laryngeal cleft
- laryngomalacia
- subglottic cyst
- tracheomalacia

You selected 2, the correct answer is 1.

Stridor is produced by a rapid, turbulent flow of air through a narrowed segment of the airway. It is an important sign of airway obstruction in infants and children. Stridor may be classified as inspiratory, expiratory, or biphasic. Inspiratory stridor typically is produced by an obstruction at or above the level of the vocal cords. Biphasic stridor most commonly occurs with obstruction at the glottic or subglottic level. The subglottic lumen is surrounded by the cricoid cartilage, which is the only fixed ring of cartilage in the airway. Inspiration and expiration produce similar turbulent flow when this area is obstructed, resulting in biphasic stridor. Expiratory stridor most commonly is produced by an intrathoracic site of airway obstruction.

In addition to stridor, other physical findings consistent with airway obstruction include retractions, especially with glottic and supraglottic disease, hoarseness, tachypnea, nasal flaring, difficulty feeding, intermittent cyanosis, and failure to thrive.

The differential diagnosis of congenital stridor includes laryngomalacia, tracheomalacia, bilateral vocal cord paralysis, subglottic stenosis, and a variety of obstructing lesions, such as tumors or cysts. Laryngomalacia is by far the most common cause of congenital stridor, occurring in approximately 70% to 80% of patients who have stridor. It is characterized by an intermittent whooping, late inspiratory stridor that typically involves no respiratory distress. Vocal cord paralysis is the second most common cause of stridor. Unilateral paralysis may cause a hoarse, breathy voice, but it rarely causes airway distress. Bilateral vocal cord paralysis presents with inspiratory stridor that often is severe and is associated with retractions and blue spells. The cry may be normal or weak, as described for the infant in the vignette.

Subglottic stenosis manifests as biphasic stridor with no voice abnormalities and may be congenital or acquired following intubation. Subglottic cysts also can occur after intubation. They rarely are present at birth, and commonly they cause progressive stridor 1 to 2 months after intubation. The stridor is typically biphasic and may be associated with voice abnormalities.

Laryngeal cleft is a rare congenital defect of the posterior larynx in which the dorsal aspect of the cricoid cartilage or trachea fails to fuse. Laryngeal clefts can be
associated with stridor if there is concomitant subglottic stenosis or redundancy of supraglottic tissues. Most commonly, laryngeal clefts cause aspiration, recurrent respiratory infections, difficulty swallowing, and choking spells. Tracheomalacia, or flaccidity and collapse of tracheal cartilage, classically is associated with expiratory stridor. Usually there are no abnormalities of the voice. In severe cases, failure to thrive and cyanosis may be present.

The severe congenital inspiratory stridor that is associated with retractions and a weak cry, as described for the infant in the vignette, suggests the diagnosis of vocal cord paralysis. An accurate diagnosis usually can be made by flexible upper airway endoscopy with visualization of the larynx and trachea. Flexible endoscopy can be used to assess the supraglottic larynx and to diagnose both laryngomalacia and vocal cord paralysis. The subglottic lumen, however, may be difficult to assess with this technique. Tracheomalacia is readily apparent on either flexible or rigid bronchoscopy.

Airway fluoroscopy can be useful in diagnosing vocal cord paralysis and tracheomalacia. Supraglottic abnormalities such as laryngomalacia are difficult to determine on radiography. Microlaryngoscopy and rigid bronchoscopy in the operating room often are required to make a diagnosis of laryngeal cleft or significant subglottic stenosis. A barium swallow may demonstrate aspiration in a cleft larynx. Vascular rings (eg, double aortic arch [Figure 26A], retroesophageal subclavian) cause esophageal compression that may be noted on barium swallow. Magnetic resonance imaging or computed tomography of the chest also can be performed to evaluate the thoracic vascular anatomy.

References:
Holinger LD. Etiology of stridor in the neonate, infant and child. Ann Otol Rhinol Laryngol. 1980;89:397-400

Content specification(s)
Know the various causes of stridor in the newborn
A newborn has respiratory distress, with difficulty breathing at rest and an inability to feed. He has a normal, vigorous cry, which relieves the distress, and no stridor. Physical examination reveals no obvious anomalies.

Of the following, the MOST appropriate procedure to lead to the presumptive diagnosis is:

1. airway fluoroscopy to evaluate vocal cord mobility
2. an attempt to pass a catheter through the nose into the nasopharynx
3. anteroposterior neck radiographs to assess subglottic lumen diameter
4. barium esophagography to exclude vascular ring
5. examination of the oral cavity for retrognathia and glossoptosis

You selected 5, the correct answer is 2.

Respiratory distress in the newborn may be caused by obstruction at any point in the airway. Newborns who have nasal obstruction and a normal distal airway will have respiratory distress when the mouth is closed and feeding difficulties. A normal, vigorous cry and adequate airway with the mouth open, as described for the infant in the vignette, suggests a normal distal airway. Obstruction at the level of the oropharynx and hypopharynx typically manifests as inspiratory stridor. The stridor persists when the mouth is closed. Obstruction at the level of the glottis or subglottis classically causes biphasic stridor, often with retractions and an abnormal, weak, or hoarse cry if the vocal cords are involved. Tracheal obstruction classically manifests as expiratory stridor.

The most common cause of congenital nasal obstruction is choanal atresia, which occurs in 1 in 7,000 live births. It is slightly more common among females and usually is unilateral. Most cases are mixed bony-membranous atresias. Approximately 50% of patients have associated anomalies, one of the most common of which is the CHARGE association that involves anomalies of choanal atresia, colobomas of the retina, cardiac defects, genitourinary anomalies, mental retardation, and hearing loss.

Bilateral choanal atresia with complete nasal obstruction results in immediate onset of respiratory distress in newborns. Unilateral choanal atresia rarely causes acute respiratory distress, but often presents later in life with unilateral thick rhinorrhea that does not improve with medications.

The initial diagnostic procedure of choice to evaluate for choanal atresia is to pass a #6 French catheter or dilator through the nose into the oropharynx. Failure of the catheter to pass through the nose suggests the diagnosis, which can be confirmed by flexible endoscopy. Computed tomography (CT) in the axial plane is recommended prior to surgical intervention.

Most infants who have choanal atresia require immediate intervention with an oral airway. Once they are stabilized and the diagnosis is confirmed with CT scan, operative repair is performed. Most commonly, endoscopic procedures are used to open the atresia plate. Stenting of the nasal airway sometimes is needed postoperatively.
Retrognathia and glossoptosis associated with cleft of the secondary palate is a description of Pierre Robin sequence, previously called the Pierre Robin syndrome. Affected infants have upper airway obstruction and feeding difficulties because of the glossoptosis. Airway obstruction may be present, even with crying. Vascular rings may cause tracheal and esophageal compression. Expiratory stridor with respiratory distress that is unrelieved with crying and dysphagia are typical manifestations.

Subglottic stenosis presents with biphasic stridor and respiratory distress. Stridor is more pronounced with agitation and crying. Bilateral vocal cord paralysis also presents with predominantly inspiratory, but occasionally biphasic stridor. Because the vocal cords typically are paralyzed in the paramedian position, the cry may be normal, but crying and agitation increase stridor and respiratory distress.

Several other conditions may produce symptoms similar to those reported for choanal atresia. Anterior pyriform aperture stenosis, with narrowing of the front of nose, is seen occasionally. The formation of cysts of the distal aspect of the nasal lacrimal duct (nasal lacrimal duct cyst) can obstruct the nose and cause respiratory distress. Rhinitis of infancy, an idiopathic inflammation of the nose, can present with nasal obstruction that mimics choanal atresia. In all of these conditions, catheters typically can be passed into the oropharynx.

References:

Content Specification(s):
Recognize the incidence, clinical manifestations, and treatment of bilateral and unilateral choanal atresia
An otherwise healthy newborn male has retrognathia, glossoptosis, and U-shaped cleft of the posterior palate. Over the first 2 weeks of life he experiences frequent episodes of obstructive apnea with desaturation, bradycardia, and an inability to feed.

Of the following, the MOST appropriate treatment at this time is placement of a

- gastrostomy tube
- mandibular prosthesis
- nasogastric tube
- palatal prosthesis
- tracheotomy tube

You selected 3, the correct answer is 5.

Pierre Robin sequence includes micrognathia, glossoptosis with downward posterior displacement of the tongue, and U-shaped cleft of the soft palate, as described for the infant in the vignette. The initial event in the sequence is failure of mandibular growth with retrognathia. Retrodisplacement of the tongue and failure of the palatal shelves to close result in a classic U-shaped cleft. Pierre Robin sequence may occur as an isolated anomaly or may be associated with other syndromes, including Stickler syndrome, velocardiofacial syndrome, and CHARGE association.

Retrognathia and glossoptosis can cause partial airway obstruction in some children, which is exacerbated by supine positioning. Significant desaturations and bradycardia occur in a small percentage of infants, and feeding difficulties are common. Posterior displacement of the tongue and the presence of a cleft may result in a poor suck and disorganized swallowing. The majority of affected patients (up to 85%) can be managed conservatively with positioning. Placing the infant in a prone or partially prone position allows the tongue to fall forward, which can relieve the airway obstruction. Supplemental oxygen occasionally is required. Between 10% and 15% of patients continue to have life-threatening events, with desaturations, bradycardia, and inability to feed despite optimal nursing care. The need for airway or feeding intervention is more common among patients who have Pierre Robin sequence in association with other anomalies.

The treatment of choice in patients who have severe airway problems is elective tracheostomy, which bypasses the upper airway obstruction and allows patients to feed. Other described procedures include lip-tongue adhesion in which the tongue is sutured anteriorly to the lower lip in an attempt to prevent glossoptosis. Gastrostomy tube feeding is necessary in some patients who fail to feed with tracheostomy, but it is not the initial treatment of choice for infants who have obvious airway obstruction. Nasogastric tube feeding may be appropriate for initial management of patients who have Pierre Robin sequence, but it does not treat the respiratory events. Palatal prostheses are used in those who have wide clefts and feeding difficulties to improve sucking and swallowing, but the added obstruction from a palatal obturator actually may increase the risk of airway events in infants who have Pierre Robin sequence. Mandibular prosthetics are not appropriate,
although surgical mandibular advancement has shown promising results in a small number of patients.

References:


Content Specification(s):

Know the associations and clinical manifestations of macroglossia and hypoplastic mandible

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A 7-week-old 1,100-g male infant, whose birthweight was 620 g and estimated gestational age at birth was 25 weeks, presents with acute worsening of ventilatory status. His clinical course to date has been characterized by initial respiratory distress syndrome, recurrent apnea, *Klebsiella* sepsis, grade 1 germinal matrix hemorrhage, and prolonged ventilator dependence. A trial off of mechanical ventilation was planned until his clinical condition worsened approximately 5 days ago. He is receiving furosemide, aerosolized bronchodilator, inhaled beclomethasone, midazolam, and morphine. Antibiotic treatment is started after blood and tracheal aspirate specimens are obtained for culture. Physical examination reveals diminished breath sounds with crackles and wheezes throughout all lung fields and a barrel-shaped chest. Although the infant is breathing in synchrony with the ventilator, the ventilator breath appears to interrupt exhalation. The ventilator settings in the volume mode are:

Tidal volume: 6 mL/kg  
Ventilator rate: 52 breaths/min  
Inspiratory time: 0.35 sec  
Peak inspiratory pressure: 36 cm H2O  
Positive end-expiratory pressure: 6 cm H2O  
Pressure support: 15 cm H2O

Scalar flow diagram, pressure-volume loop, and flow-volume loop are shown in Figures 1 through 3.

**Figure 1.** Scalar Monitoring of Flow Waveform

![Scalar Monitoring of Flow Waveform](image1)

**Figure 2: Pressure-Volume Loop**

![Pressure-Volume Loop](image2)
The chest radiograph is shown in Figure 4.

An arterial blood gas reveals: pH, 7.23; Paco₂, 82 mm Hg; Pao₂, 33 mm Hg; base...
excess, 9 mEq/L; and bicarbonate, 28 mEq/L (28 mmol/L).

Of the following, the ventilatory adjustment MOST likely to correct the respiratory insufficiency in this infant is a

1. decrease in tidal volume
2. decrease in ventilator rate
3. increase in inspiratory time
4. increase in positive end-expiratory pressure
5. increase in pressure support

You selected 3, the correct answer is 2.

Chronic lung disease, or bronchopulmonary dysplasia, is a complication of prematurity. Although prematurity is the principle underlying factor for this disorder, a variety of other factors contribute to its pathogenesis. These factors include volutrauma, barotrauma, atelectasis, oxygen toxicity, respiratory distress syndrome, pulmonary edema, inflammation, infection, impaired wound healing, chronic aspiration, increased airway resistance, bronchoconstriction, pulmonary vascular injury, and pulmonary hypertension. Histopathology of the lung in bronchopulmonary dysplasia reveals emphysema, atelectasis, and coalescence of air spaces; widespread mucosal hyperplasia and resultant narrowing of small airways; interstitial edema, fibrosis, and dilated lymphatics; and in severe cases, pulmonary vascular medial muscle hypertrophy and reduction in the size of the pulmonary vascular bed.

Pulmonary function in neonates who have bronchopulmonary dysplasia is characterized by variable lung volume, low compliance, increased airway resistance, and increased airway reactivity. Ventilation/perfusion mismatching, alveolar hypoventilation, and increased alveolar dead space contribute to respiratory compromise and resultant hypoxemia, hypercapnia, increased work of breathing, and tachypnea. Episodic increases in airway resistance and bronchoconstriction also are characteristic of bronchopulmonary dysplasia, especially if exacerbated by infection or aspiration. The infant described in the vignette has acute worsening of his ventilatory status, possibly related to severe bronchospasm due to silent aspiration and pneumonia.

The ventilatory adjustment most likely to correct the respiratory insufficiency in the infant is a decrease in the ventilator rate. The symptoms and signs described for the infant are consistent with bronchoconstriction and air trapping. Gas trapping results in increased lung volume and pressure within the alveoli and distal airways. This pressure build-up is termed inadvertent positive end-expiratory pressure (inadvertent PEEP). Because inadvertent PEEP is not reflected at the proximal end of the endotracheal tube where pressure usually is measured, it must be assessed using information from chest radiographs and measurements of lung mechanics, waveforms, pressure-volume loops, and flow-volume loops.

The flow waveform for this infant demonstrates that he is beginning inspiration before exhalation is completed or trapping air (Figure 5).

Figure 5. Respiratory Mechanics: Scalar Monitoring of Flow Waveform in Bronchopulmonary Dysplasia
The pressure-volume loop demonstrates a "beaking" or flattening of the pressure-volume loop at the end of inspiration, which is consistent with air trapping, overdistension, and reduced compliance (Figure 6).

**Figure 6: Pressure-Volume Loop in Bronchopulmonary Dysplasia (BPD)**

Furthermore, the increased expiratory resistance associated with small airway disease and bronchospasm is evidenced by a prolonged period of high pressure during exhalation (increased hysteresis).

The flow-volume loop demonstrates abrupt airflow limitation during exhalation, which is consistent with obstructive airway disease (Figure 7).

**Figure 7. Flow-Volume Loop in Bronchopulmonary Dysplasia (BPD)**
Inadvertent PEEP alters the elastic and resistive forces within the lung and must be considered when managing neonates receiving mechanical ventilation. The relationship between the elastic and resistive forces on the lung determines the amount of time required for lungs to inhale and exhale or for alveolar and proximal airway pressures to equilibrate. This relationship is termed the time constant of a patient’s respiratory system. Furthermore, exhalation of the lung is driven by the elastic recoil of the lung and chest wall, and the elastic recoil of the lung is inversely related to compliance (C). The major force resisting exhalation is airway resistance (R). Therefore, the expiratory time constant is related directly to the compliance and the resistance of the lung, as shown by the equation: Expiratory Time Constant (sec) = C (L/cm H2O) × R (cm H2O/L per second).

The infant in the vignette has bronchopulmonary dysplasia and air trapping from bronchoconstriction and airway edema, which has caused CO2 retention. The intuitive response is to increase minute ventilation by increasing ventilator rate, tidal volume, pressure support, or all three on the ventilator. However, airway mechanics waveform and respiratory loop analysis indicate high airflow resistance, which prolongs the expiratory time constant or amount of expiratory time during the mechanical ventilator breaths needed to allow sufficient time for exhalation. Interventions that increase expiratory time include decreasing the ventilator rate while maintaining the same inspiratory time, decreasing the inspiratory time while maintaining the same ventilator rate, or a combination of these approaches as well as medications such as bronchodilators and corticosteroids that reduce bronchoconstriction. For this infant, the inspiratory time is relatively short, and reducing it may decrease mean airway pressure and impair oxygenation. Therefore, reducing ventilator rate, rather than inspiratory time, is preferred.

Decreasing the respiratory rate and prolonging expiratory time reduces lung overdistension and increases compliance, thereby increasing alveolar ventilation and gas exchange. At times, the effect of reducing the respiratory rate in this circumstance can be dramatic. Additional aerosolized bronchodilator; sedation/analgesia; switch to time-cycled, pressure-limited ventilation mode with continuous flow; or pharmacologic paralysis may have similar rapid effects on gas exchange. Although theoretically helpful, inhaled nitric oxide and other pulmonary vasodilators have yet to be proven beneficial during acute exacerbations of bronchopulmonary dysplasia complicated by pulmonary hypertension. Other medical interventions whose effects have a slower onset of action include systemic steroids, vitamin A supplementation, and additional bronchodilator and diuretic therapy.

Decreasing tidal volume can reduce minute ventilation in this infant and worsen...
respiratory acidosis. Mean airway pressure also will be reduced, which would lead to worsening hypoxemia unless cardiovascular function has been compromised on the current settings. Chest radiography does not show a small heart shadow, a sign of potential cardiac compromise with lung overdistension, but it does suggest that cardiac function is not affected severely by the current ventilator support. Increasing tidal volume increases lung volume, which has the potential to worsen air trapping and hyperexpansion.

Increasing inspiratory time without changing other ventilator settings shortens the expiratory time. Shortening expiratory time in the presence of air trapping and lung overdistension can compromise alveolar ventilation further. Mean airway pressure increases and oxygenation may improve, but this change depends on the impact of additional mean airway pressure on atelectasis, pulmonary edema, and cardiovascular function.

Increasing PEEP, whether by setting a higher PEEP or with inadvertent PEEP, may increase hyperexpansion, thereby exacerbating CO2 retention. The impact of PEEP (set PEEP + inadvertent PEEP) on gas exchange is monitored by the effects on mean airway pressure and oxygenation, respiratory mechanics, and ventilation. In clinical situations complicated by lung hyperexpansion, mean airway pressure may be high and oxygenation adequate as long as cardiovascular function is not compromised, but with hyperexpansion, compliance is reduced and ventilation is impaired. If venous return and cardiac output are impaired by high mean airway pressure in a patient who has air trapping, oxygenation suffers. In this situation, reducing PEEP and mean airway pressure improves oxygenation while simultaneously increasing the driving, or ventilatory, pressure (peak inspiratory pressure - PEEP) and lessening CO2 retention. Because variable amounts of segmental atelectasis, hyperexpansion, and pulmonary edema characterize bronchopulmonary dysplasia in preterm infants from hour to hour, the impact of any intervention must be monitored closely for untoward effects and titrated based on response.

Increasing pressure support is an alternative for neonates who are breathing spontaneously in addition to receiving ventilator breaths. However, the infant in the vignette is breathing with the ventilator, and increasing the pressure support would have no effect on ventilation.

The complexity and variability of bronchopulmonary dysplasia in preterm infants requires interpretation of many variables that affect ventilation and oxygenation simultaneously and, at times, differently. The physiologic principles illustrated in this case should be considered with the understanding that they are important guides for interventions, but are limited by the complexity of bronchopulmonary dysplasia and variable benefits and risks of the interventions available. The care of each baby requires individualization and adaptation as the pathophysiology changes.

References:


Content Specifications:

Understand the physical principles governing gas flow, including the ventilatory significance of short and long time constants

Plan the ventilatory therapy for infants with respiratory failure of different etiologies
Understand the indications for and techniques of positive-pressure ventilation (PPV)

Understand the effects and risks of PPV

Understand the pathogenesis and pathophysiology of bronchopulmonary dysplasia/chronic lung disease

Understand the risk factors for bronchopulmonary dysplasia/chronic lung disease

Recognize the clinical features of bronchopulmonary dysplasia/chronic lung disease

Recognize the laboratory features of bronchopulmonary dysplasia/chronic lung disease

Recognize the radiographic features of bronchopulmonary dysplasia/chronic lung disease

Recognize the pathologic features of bronchopulmonary dysplasia/chronic lung disease

Understand the prevention of bronchopulmonary dysplasia/chronic lung disease

Understand the management of bronchopulmonary dysplasia/chronic lung disease

Know factors that determine residual lung volume, functional residual capacity, and tidal volume, and how they change with various pulmonary disorders

Recognize the factors that alter lung compliance and chest wall compliance and how they change with various pulmonary disorders and with gestational age

Understand the factors that affect airway resistance and how resistance changes with various lung disorders
A 900-g male infant is born to a 28-year-old primiparous woman at 26 weeks of estimated gestational age following spontaneous preterm labor and precipitous vertex vaginal delivery. The mother did not receive antenatal steroids. The infant has marked intercostal and subcostal retractions and cyanosis. Endotracheal intubation is performed, and mechanical ventilation is started using a time-cycled, pressure-limited mode with the following settings:

- Fio2: 0.8
- Ventilatory rate: 40 breaths/min
- Peak inspiratory pressure: 16 cm H₂O
- Positive end-expiratory pressure: 5 cm H₂O
- Pressure support: 10 cm H₂O
- Inspiratory time: 0.3 sec

Surfactant is not available for immediate administration. At 26 minutes of age, the infant has a respiratory rate of 72 breaths/min and oxygen saturation of 78%. The arterial blood gas measurement shows: pH, 7.21; Pco₂, 68 mm Hg; Po₂, 39 mm Hg; and base excess of -3 mEq/L. The tidal volume is 3 mL with ventilator breaths and 2 mL with pressure support breaths. Chest radiography and pressure-volume loops are obtained.

Of the following, the respiratory management adjustment measure that is MOST likely to improve the ventilatory status of this infant is to:

1. decrease positive end-expiratory pressure
2. decrease pressure support
3. extubate to continuous positive airway pressure
4. increase peak inspiratory pressure
5. induce pharmacologic paralysis

You selected 4, the correct answer is 4.

The preterm infant described in the vignette did not receive antenatal steroids and is male, both of which are risk factors for respiratory distress syndrome (RDS) or hyaline membrane disease. RDS is characterized by primary surfactant deficiency and immature lung morphology.

Primary surfactant deficiency results in collapse of respiratory bronchioles, alveolar saccules, and alveoli, with resultant loss of lung volume. When respiratory bronchioles collapse before alveoli, air is trapped, with subsequent resorption of trapped gas and atelectasis. Surfactant can stabilize respiratory bronchioles, alveolar saccules, and alveoli by modulating surface tension, which is the primary contributing force for elastic recoil and exhalation in the neonatal lung. Without surfactant, small alveoli empty into larger alveoli, according to the Laplace relationship. The Laplace relationship states that the distending pressure required to stabilize alveoli is directly proportional to twice the surface tension (ST) and inversely proportional to the radius (r): [Pressure = 2 x ST/r]. Therefore, small surfactant-deficient alveoli require a higher distending pressure to remain open than do larger surfactant-deficient alveoli. If the distending pressure is not equilibrated by surfactant, the small alveoli collapse as gas moves into larger alveoli. The physiologic effect of
surfactant deficiency is loss of gas volume within the lung. Functional residual capacity (the volume of gas in the lung at the end of exhalation) is reduced and may decrease below the closing, or collapsing, volume of the lung. Without an appropriate functional residual capacity, the reservoir of gas available to supply oxygen for energy production is impaired. Loss of lung volume also impedes ventilation because compliance, or the change in lung volume resulting from changes in alveolar pressure, is reduced. Low compliance requires increased work of breathing and may exhaust respiratory muscle energy stores, which may result in respiratory acidosis. Clinically, loss of lung volume is indicated by retractions, grunting respirations, tachypnea, and cyanosis. Chest radiography demonstrates a reticulogranular pattern and low lung volumes, as reported for the infant in the vignette. Flattened pressure volume loops also indicate low compliance and low lung volume.

Immature lung structure also contributes to the pathophysiology of RDS. The lung development in preterm infants born between 26 and 36 weeks of gestation is in the terminal sac phase. During this phase, primary alveolar saccules and respiratory bronchioles formed during the canalicular phase divide further into subsaccules and alveoli, thick interstitial connective tissues continue to dissipate, and alveolar capillaries proliferate to increase the alveolar-blood barrier surface area. Preterm infants, especially those born extremely preterm, are compromised by limited numbers of alveolar saccules and capillary beds for gas exchange as well as diffusion barriers caused by thick interstitium. Physiologic compensation for surfactant deficiency and lung immaturity is compromised further in the preterm infant who has an unstable and cylindrical chest wall, horizontal diaphragm position, and immature respiratory drive.

The therapeutic measure most likely to improve the ventilatory status of the infant in the vignette is to increase the peak inspiratory pressure. The arterial blood gas findings indicate acute respiratory acidosis and hypoxemia. The tidal volume (3 mL/kg) is low and inadequate to provide sufficient minute ventilation (tidal volume x respiratory rate) to correct the respiratory acidosis. Hypoxemia also is present, despite a high Fio₂ of 0.8, and could be improved by increasing the Fio₂, but the respiratory acidosis would not be changed, and oxygen toxicity could be worsened. When oxygen toxicity is of more concern than barotrauma, adjusting mechanical ventilation to increase mean airway pressure is a reasonable therapeutic option. Therefore, it is appropriate to increase minute ventilation to correct respiratory acidosis and increase the mean airway pressure to improve oxygenation by increasing the peak inspiratory pressure for this infant. The increase in minute ventilation lowers the Paco₂, and the increase in mean airway pressure increases oxygenation. These predicted changes are based on an unchanged severity of RDS.

Decreasing positive end-expiratory pressure lowers mean airway pressure and subsequent lung volume. The ventilatory pressure difference, or delta P (peak inspiratory pressure - positive end-expiratory difference), widens with a decrease in positive end-expiratory pressure. If the lung volume remains unchanged, such an increase in ventilatory pressure difference increases tidal volume and lowers the Paco₂. However, the lung volume of the infant in the vignette already is low; additional reduction would exacerbate the pathophysiology of RDS, resulting in hypoxemia and respiratory acidosis.

Increasing positive end-expiratory pressure could increase lung volume and increase compliance. However, recruitment of lung volume with positive end-expiratory pressure alone in the absence of maneuvers to open the gas exchange units (eg, increases in peak inspiratory pressure or inspiratory time, sigh breaths) frequently is too slow during severe respiratory failure, as described for the infant in the vignette.

Reducing pressure support during spontaneous respiratory efforts decreases minute ventilation and worsens respiratory acidosis. The baby in the vignette is contributing substantially to his own respiratory efforts by breathing with pressure support at a
rate of 72 breaths/min; lowering the pressure support would lower the tidal volume during these spontaneous breaths.

Extubation to continuous positive airway pressure in an extremely preterm infant who has severe respiratory failure is not a preferred treatment option. A preterm male infant who has not received antenatal steroids and treatment with exogenous surfactant is at high risk for progressive respiratory failure associated with RDS. RDS usually worsens and peaks in severity at 2 to 3 days of age without the previously noted interventions. Therefore, in the face of severe respiratory failure shortly after birth, continuous positive airway pressure would not support the respiratory status adequately.

Pharmacologic paralysis removes the infant’s spontaneous respiratory contributions to gas exchange and reduces chest wall stability by paralyzing the intercostal and accessory muscles. Respiratory acidosis and hypoxemia could worsen without compensatory increases in ventilatory and oxygen support.

References:


Content Specifications:

Understand the effects of surface tension on alveolar and airway stability and lung mechanics (LaPlace Law)

Understand the timing of the biochemical maturation of the lung and the factors affecting this timing

Know the factors that determine residual lung volume, Functional residual capacity, tidal volume and how they change with various pulmonary disorders

Recognize the factors that alter lung compliance and chest wall compliance and how they change with various pulmonary disorders and with gestational age

Understand the pathophysiology of RDS

Understand the risk factors of RDS

Understand the clinical features of RDS

Understand the radiographic feature of RDS

Understand the management of RDS, including surfactant replacement
A 1,920-g female infant is born at 42 weeks' gestation to a 33-year-old multiparous (gravida 8, para 7) woman, whose pregnancy is complicated by the absence of prenatal care and the use of crack cocaine. The delivery is by emergent cesarean section prompted by vaginal bleeding and fetal distress. Meconium-stained amniotic fluid is present at delivery. The infant has a heart rate of 60 beats/min, no spontaneous respiration, generalized cyanosis, poor muscle tone, and decreased reflex irritability. Endotracheal intubation is performed, and a large amount of thin meconium is suctioned. After bag-and-mask ventilation with an Fio2 of 1.0 for 2 minutes, the infant has a normal heart rate, muscle tone, and reflex irritability. Her respiratory rate is 82 breaths/min. She requires oxygen by mask (Fio2 of 1.0) to remain pink with an oxygen saturation of 94%. Chest radiography shows patchy infiltrates and normal-to-high lung volume; heart size and vascularity appear normal (Fig. 1).

Of the following, the pathophysiologic event affecting the lung that is MOST likely to occur in this infant is

- [ ] airway epithelial necrosis
- [ ] eosinophilic cell infiltration
- [ ] interleukin-8 suppression
- [x] pulmonary hemorrhage
- [ ] surfactant function augmentation

You selected [x], the correct answer is [1].

The infant described in the vignette has meconium aspiration syndrome. Meconium is the first bowel movement of the newborn. It is a viscous green or black liquid that is composed of gastrointestinal secretions, cellular debris, bile and pancreatic juices, mucus, blood, lanugo, and vernix. Meconium may be passed in utero and aspirated during fetal gasping efforts or aspirated postnatally. Meconium aspiration is associated with a complex array of pathophysiologic events, including mechanical obstruction of airways, chemical pneumonitis, surfactant dysfunction, and pulmonary hypertension. Any one or all of these pathophysiologic abnormalities may contribute to the disorder in affected infants. Therefore, interventions must be individualized.

Complete mechanical obstruction of airways leads to segmental air trapping, resorption of trapped air, atelectasis, and decreased compliance (Fig. 2). Partial mechanical obstruction mimics a ball-valve effect in which gas flows into distal lung segments during inspiration as the airways distend, but the gas flow is obstructed during expiration as the airways narrow. This ball-valve effect leads to overdistension of distal lung segments, pneumothorax, gas trapping, and decreased compliance (Fig. 2). Secondary surfactant dysfunction due to the direct effect of meconium on surfactant or indirect effects through intra-alveolar inflammation and proteinaceous debris may cause atelectasis and segmental decreases in compliance. Pulmonary hypertension frequently is associated with severe meconium aspiration, although its cause-and-effect relationship remains unestablished. Pulmonary vasoconstriction may cause right-to-left shunting at the foramen ovale and ductus arteriosus and result in hypoxemia. Pulmonary vasoconstriction makes pulmonary hemorrhage unlikely. Because of the segmental nature and variety of
pathophysiologic factors operating in meconium aspiration syndrome, choosing appropriate mechanical ventilation strategies and treatment interventions such as surfactant, inhaled nitric oxide, and extracorporeal membrane oxygenation are challenging.

The pathophysiologic event affecting the lung that is most likely to occur in meconium aspiration syndrome is airway epithelial cell necrosis, which is most evident within 8 to 24 hours after exposure of the lung to debris-free meconium fluid. Airway epithelial cells respond to meconium by rounding, swelling, and sloughing into the airways. Furthermore, a threefold increase in dead cells, increased neutrophilic cells, and high levels of inflammatory cytokines are found in lung lavage specimens within hours of meconium exposure.

Eosinophils are not identified commonly in the inflammatory course of meconium aspiration syndrome. The predominant cells in the inflammatory exudate are macrophages and polymorphonuclear leukocytes.

Interleukin-8 (IL-8) is an inflammatory cytokine that is found in high quantities in the lungs of animal models of meconium aspiration syndrome. Similarly, tumor necrosis factor, IL-B1, and prostaglandin E2 concentrations are elevated, whereas concentrations of IL-10, an anti-inflammatory cytokine, are unchanged.

Surfactant function is inhibited, not enhanced, by meconium. Other proteinaceous materials from injured epithelial cells and inflammation within the respiratory units of the lung that result from meconium aspiration also have been shown to disturb surfactant function.

References:


Content Specification(s):

1586. Know the pathogenesis, pathophysiology, and risk factors of meconium aspiration syndrome
2292. Recognize the clinical features of meconium aspiration syndrome
2293. Recognize the laboratory, radiographic, and pathologic features of meconium aspiration syndrome
A 1-day-old infant appears dusky during feeding. Oxygen is administered via nasal cannula, and 2 hours later she develops tachypnea. Findings include: heart rate, 170 beats/min; respiratory rate, 80 breaths/min; right arm blood pressure, 48/30 mm Hg; right leg blood pressure, 52/32 mm Hg; and pulse oximetry, 90% on oxygen. You suspect hypoplastic left heart syndrome.

Of the following, the MOST likely findings include

1. continuous ductal murmur, bounding pulses
2. continuous ductal murmur, poor peripheral pulses
3. holosystolic murmur, poor peripheral pulses, quiet second heart sound
4. no murmur, precordial hyperactivity, loud second heart sound
5. no murmur, precordial hyperactivity, quiet second heart sound

You selected 3, the correct answer is 3.

Infants who have hypoplastic left heart (HLH) syndrome develop signs of shock, including poor pulses and metabolic acidosis, as systemic perfusion deteriorates. Ductal closure in these infants results in inadequate blood flow to the body from the functional single ventricle because the ductus arteriosus is the only path for blood to flow from the right ventricle to the body. Even if the ductus remains open, a drop in pulmonary vascular resistance "steals" blood to the pulmonary circulation, thereby depriving the systemic circulation of adequate perfusion. For this reason, mildly cyanotic infants who have HLH syndrome often deteriorate suddenly after oxygen is administered, because the oxygen acts as a pulmonary vasodilator.

The most obvious physical findings in newborns who have HLH syndrome are a hyperdynamic precordium and a loud, even palpable single second heart sound (S2). The hyperactive precordium is due to the greatly enlarged right ventricle that is contracting against systemic pressure. The strikingly loud S2 is caused by the pulmonary artery functioning as a de facto aorta, pumping blood to the body through the ductus arteriosus. Therefore, the pulmonic closure sound is loud as a result of the high end systolic pressure found in the large pulmonary artery located just beneath the chest wall to the left of the sternum.

A continuous murmur is not heard in infants who have HLH syndrome, even though the ductus arteriosus remains open. A murmur from a ductus is created by high-velocity flow from a higher pressure aorta into a lower pressure pulmonary artery. In patients who have HLH, the pulmonary artery pressure is equal to or exceeds that of the aorta. Because flow from the systemic right ventricle to this large hypertensive pulmonary artery is not obstructed or turbulent, there is no reason for a significant murmur to occur. A holosystolic murmur will be present only if there is very significant regurgitation of the tricuspid valve, which is unusual in affected infants. Diminished peripheral pulses are a sign of HLH syndrome, particularly as the ductus starts to close or as pulmonary vascular resistance falls. Both of these changes diminish the flow of systemic blood from the main pulmonary artery through the ductus to the systemic circulation.

Maintaining ductal patency by administering an infusion of prostaglandin E1 often is not sufficient to provide adequate systemic blood flow in infants who have HLH.
syndrome. Use of the so-called "chemical banding" of the pulmonary vasculature employs ventilatory strategies to increase pulmonary vascular resistance. Administration of room air while on the ventilator (or even Fio2 less than 21% using carbon dioxide in the ventilator circuit) and muscle relaxant drugs to prevent spontaneous hyperventilation with secondary pulmonary vasodilation often can reverse metabolic acidosis and re-establish good renal and systemic perfusion after prostaglandin E1 infusion has opened the ductus arteriosus.

References:

Content Specification(s):
Recognize the clinical features of a neonate with a left-sided cardiac obstructive lesion
A 4-hour-old term male infant has persistent drooling. The infant attempted to bottle-feed and immediately choked and spit. The pregnancy was complicated by polyhydramnios. A tracheoesophageal abnormality is suspected.

Of the following, the MOST likely tracheoesophageal abnormality is:

1. esophageal atresia with a distal and a proximal tracheoesophageal fistula
2. esophageal atresia with a distal tracheoesophageal fistula
3. esophageal atresia with a proximal tracheoesophageal fistula
4. esophageal atresia without a tracheoesophageal fistula
5. tracheoesophageal fistula without esophageal atresia

You selected 3, the correct answer is 2.

Congenital esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF) is a common congenital anomaly with an incidence of 1 in 3,000 live births. Newborns with EA may present in the delivery room with either a sonorous "seal-bark" cry because of associated tracheomalacia or within the first few hours after birth with excessive oral secretions. Feeding an infant with EA will cause spitting and choking, and aspiration pneumonia can occur. Reflux of gastric secretions through a distal TEF also can cause aspiration pneumonia. Diagnosis of EA is suspected by failure to pass an orogastric tube beyond 10 cm to 11 cm from a term infant's lips. Chest radiography confirms the position of the orogastric tube in the proximal esophageal pouch.

From 30% to 60% of infants with EA and TEF have associated anomalies, including cardiac (25%), genitourinary (15%), skeletal (14%), and intestinal atresias (13%). The VACTERL association (vertebral defects, anorectal abnormalities, cardiac defects, TEF, renal abnormalities, limb defects) occurs in approximately 10% to 25% of cases.

Embryologic development of the trachea and esophagus is a complex process. During week four of gestation, the embryo is C-shaped, and the primitive (primordial) gut is divided into the foregut, midgut, and hindgut. The trachea and esophagus are formed from the foregut. The trachea develops from the laryngotracheal tube, which buds off the ventral surface of the foregut. The tracheoesophageal septum separates the foregut into tracheal and esophageal tubes. The esophagus rapidly elongates with growth of the embryo. The lumen of the esophagus becomes obliterated by the proliferation of endodermal lining cells. During week eight of gestation, endodermal cell death re-establishes the esophageal lumen. Failure of the tracheoesophageal septum to divide into the esophagus and trachea at week four of gestation, or failure of recanalization of the esophagus during week eight of gestation results in various types of EA and TEF.

Polyhydramnios may develop because the fetus with EA cannot swallow amniotic fluid. Significant polyhydramnios may lead to premature delivery in approximately 30% of cases. Because the fetus may derive some nutritional benefit from swallowed amniotic fluid, newborns with EA may be small for gestational age.

The most common tracheoesophageal abnormality (86%) is EA with a distal TEF (Fig. 1). The proximal esophagus ends blindly in the superior mediastinum at the third or fourth thoracic vertebra. The distal esophagus usually enters the posterior wall of the trachea 1 cm to 2 cm above the carina. The proximal esophageal pouch and the distal TEF may overlap or be
Education Module Learner

separated widely. Because the distal TEF allows some amniotic fluid to flow from the trachea to the gastrointestinal tract, polyhydramnios only occurs in approximately 33% of pregnancies with this type of EA.

EA with distal and proximal TEF, also known as a double TEF, is a rare (<1%) tracheoesophageal abnormality (Fig. 2). This type of malformation may be misdiagnosed as the more common EA with a distal TEF. If the small proximal TEF is unrecognized, then recurrent respiratory infections will occur. Preoperative endoscopy permits recognition of the double fistula and complete repair at the initial operation.

EA with a proximal TEF is another rare (2%) tracheoesophageal abnormality (Fig. 3). The TEF usually is located 1cm to 2cm above the distal end of the esophageal pouch. Polyhydramnios occurs nearly 100% of the time because no distal fistula is present.

Isolated EA without a TEF (Fig. 4), occurs in 7% of tracheoesophageal abnormalities. The proximal esophageal segment usually ends in the posterior mediastinum near the second thoracic vertebra. Unlike EA with distal TEF, infants without a distal TEF have a flat, gasless abdomen. A wide gap usually divides the upper and lower esophageal segments, making primary anastomosis difficult. Isolated EA without a TEF may be the result of failure of recanalization of the esophagus during week eight of gestation.

TEF without EA, also known as H-type TEF (Fig. 5), comprises 4% of tracheoesophageal abnormalities. Infants with H-type TEF may have intermittent choking episodes in the newborn period. More commonly, patients with H-type TEF present later in life, even into adulthood, with chronic cough, recurrent pneumonia, or reactive airway disease. This form of TEF is the most difficult to diagnose because the fistula may not be identified by routine contrast swallow studies. Esophagoscopy or bronchoscopy may be necessary to visualize the TEF.

References:


Content Specifications:
Know the morphogenesis of the gastrointestinal (GI) tract and factors that lead to congenital malformations
Know how to recognize and evaluate an infant with excessive gastric contents and hydramnios
Know how to diagnose polyhydramnios, its significance, and the management of pregnancy when polyhydramnios is diagnosed

Plan appropriate management for an infant with airway obstruction, such as vascular rings, choanal atresia, and tracheal abnormalities

Recognize the clinical features of VATER association
In the delivery room, you begin resuscitation of a term female infant who has apnea, bradycardia, and hypotonia. No meconium was present in the amniotic fluid. You have positioned, dried, and suctioned the nose and mouth as well as provided tactile stimulation. However, her heart rate is 50 beats per minute. You begin positive pressure ventilation (PPV) with a bag and mask.

Of the following, the MOST important clinical indicator of adequate ventilation is

- chest rise
- color
- heart rate
- muscle tone
- skin perfusion

You selected 2, the correct answer is 3.

The most important step in resuscitation of the depressed, newly born infant (heart rate <100 beats per minute, apnea or gasping respiration, hypotonia) is ventilation of the lungs. The most important response to positive pressure ventilation (PPV) is an immediate rise in heart rate. The infant in the vignette is expected to have a rapid rise in heart rate after ventilation is established. Evidence for interventions during neonatal resuscitation often is limited to comparative animal studies and consensus of opinion. Evidence that supports the heart rate response as the most important clinical indicator of response to PPV is based on animal experiments performed during the early 1960s (Figure). In these cardiorespiratory studies, changes in heart rate, breathing, and blood pressure were recorded. A rapid heart rate increase after initiation of bag and mask ventilation is followed by a gradual blood pressure increase and subsequent spontaneous respiration. Heart rate response as the most important clinical indicator of adequate ventilation is different from the frequently taught concept that chest rise is most important. Avoiding the risks associated with large tidal volume ventilation (pneumothorax and bronchopulmonary dysplasia) is an important goal that favors heart rate increase as the preferred indicator of response to PPV.

Chest rise during PPV is an indication that ventilation of the lungs is occurring. With inadvertent overventilation, the risks of volutrauma and barotrauma causing pneumothorax or initiating bronchopulmonary dysplasia in very preterm infants has caused clinicians to reassess the physiologic responses to, and technique of, ventilation with a resuscitation bag. Therefore, these risks of PPV and data from animal experiments indicate that a rapid heart rate increase, rather than chest rise, is a better indicator of adequate ventilation.

Mucus membrane color is an immediate clinical indicator of oxygenation. It follows that color will change from cyanotic to pink during the first minutes after birth in the healthy, spontaneously breathing newborn. Likewise, during PPV of an infant with bradycardia, apnea, and hypotonia, this transition to pink occurs only after ventilation of the lung with gas and establishment of cardiac output to the pulmonary and systemic circulations, both primary factors in oxygen delivery to tissues. In the neonate, heart rate appears to be more important than stroke volume to increase cardiac output.

Improved muscle tone is a sign that oxygen delivery to the brain has improved. Improved skin perfusion, on the other hand, is a sign that oxygen delivery to other organ systems also has improved. Resolution of hypotonia and improved skin perfusion are expected to follow
improvements in heart rate, establishment of lung volume and ventilation of the lung in the infant in the vignette.

References:


Dawes GS. Birth asphyxia, resuscitation and brain damage. Chicago, IL: Year Book Medical Publisher Inc. 1968:141-159


Heart Rate, Blood Pressure and Breathing after Asphyxia
A term female infant is admitted from the delivery room after resuscitation due to respiratory distress. She was delivered vaginally to a 38-year-old primigravida woman in whom fetal ultrasonography demonstrated a large nuchal translucency measurement and moderate bilateral pleural effusions, and a fetal karyotype showed three copies of chromosome 21. At birth, the infant exhibited no hydrops, congestive heart failure, or congenital heart disease.

Of the following, the pathophysiologic consideration that MOST likely caused the pleural effusions in the infant is

- increased pulmonary venous pressure
- increased systemic venous pressure
- maldevelopment of the lymphatic system
- perforation of the parietal pleura
- thoracic duct injury

You selected 2, the correct answer is 2.

The pleural space lies between the parietal pleura of the chest wall and visceral pleura of the lungs. Normally, little fluid accumulates in the pleural space because production of pleural fluid by both parietal and visceral pleura is matched by reabsorption through lymphatics located in the connective tissue lying immediately below the pleural surface. Fluid does accumulate when the balance between pleural fluid filtration and absorption is altered. Filtration pressure increases when systemic venous pressure and pulmonary venous pressure are elevated and when permeability increases due to infection. Pleural fluid absorption and clearance are decreased when systemic venous pressure obstructs drainage of the thoracic duct into the venous circulation or there is congenital obstruction of thoracic vessels with lymphatic fistula formation into the pleural space. Treatment of the hydrothorax and chylothorax includes expectant management, use of formulas containing medium-chain triglycerides (decreases thoracic duct flow), withholding of oral feedings, direct needle or thoracostomy drainage, pleuroperitoneal shunt drainage, or continuous infusion of somatostatin.

The infant described in the vignette has trisomy 21, which was suggested antenatally by the combination of elderly maternal age and wide nuchal translucency in the fetus on prenatal ultrasonography and confirmed on the fetal karyotype. Infants who have trisomy 21 are known to have malformations in the lymphatic system that may cause fetal and neonatal pleural effusions. Similar lymphatic abnormalities occur in infants who have Turner and Noonan syndromes.

Increased pulmonary and systemic venous pressure may occur with congestive heart failure, hydrops, congenital anomalies of the lymphatic system, or mechanical obstruction of the thoracic duct with central venous catheters or thrombi. The visceral pleura is drained by the pulmonary veins, and the parietal pleura is drained by systemic veins. Increased pressure in either of these venous systems can obstruct venous drainage, increase venous pressure, and result in increased filtration pressure by the visceral and parietal pleura. If lymphatic clearance cannot compensate for increased pleural fluid production, pleural effusion develops. Heart failure, hydrops, or mechanical obstruction of the thoracic duct that could increase pulmonary and systemic venous pressures were not present in the infant in the vignette.

Direct perforation of the parietal pleura by a central venous catheter or diffusion of hypertonic solutions from central catheters into the pleural space also can cause pleural effusions with
intravenous fluids in neonates. Pericardial effusion and tamponade occasionally accompany pleural effusions caused by these mechanisms. Acute decompensation may require immediate pleural or pericardial drainage.

Thoracic duct injury may occur following cardiothoracic surgery (eg, for congenital heart disease, congenital diaphragmatic hernia, ductus arteriosus), extracorporeal membrane oxygenation, or deep insertion of thoracostomy tubes. Unilateral and bilateral pleural effusions may result from drainage of lymphatic fluid directly into the pleural space.

References:


Content Specification:

Understand the pathophysiology and recognize the clinical, radiographic and laboratory manifestations of hydrothorax/chylothorax.
You are examining a 28-hour-old female infant who was born at 41 weeks’ gestation and had meconium aspiration syndrome. On physical examination, she has normal blood pressure, pink color, normal perfusion, and mild hypotonia. She responds to touch and has no dysmorphic features. She is asleep and breathing with the oscillation of the ventilator. She is being treated with a fraction of inspired oxygen (Fio₂) of 1.0, high-frequency oscillation (mean airway pressure, 21 cm H₂O; frequency, 8 Hz; power, 48 cm H₂O), fentanyl, surfactant, dopamine, epinephrine, and dexamethasone. Chest radiography shows patchy infiltrates scattered throughout the lung fields and lungs expanded to the ninth rib in the right hemithorax. Umbilical arterial blood gas measurements are: pH, 7.31; Paco₂, 46 torr; Pao₂, 48 torr; and base excess, 0 mEq/L. Oxygen saturation in the right hand and right foot is 93% and 86%, respectively.

Of the following, the intervention that is MOST likely to improve oxygenation with the least risk for this infant is

- extracorporeal membrane oxygenation
- high-frequency jet ventilation
- inhaled nitric oxide
- liquid ventilation
- surfactant lavage

You selected 4, the correct answer is 3.

A complex array of pathophysiologic disturbances occurs after meconium is aspirated into the lungs of newborns. Mechanical obstruction of airways, chemical pneumonitis, surfactant dysfunction, and pulmonary hypertension contribute to segmental hyperexpansion and atelectasis, ventilation-perfusion mismatching, inflammation, and right-to-left shunting through the foramen ovale or ductus arteriosus. Hypoxemia, hypercarbia, and respiratory acidosis may occur.

Supplemental oxygen and mechanical ventilation are used to maintain acceptable oxygenation and ventilation goals. The infant described in the vignette is poorly oxygenated, despite acceptable ventilation and acid-base balance with an Fio₂ of 1.0; high settings on high-frequency oscillation; administration of surfactant; and cardiac output supported by dopamine, epinephrine, and dexamethasone. The oxygenation index (OI), which quantifies the oxygenation response for the level of mechanical ventilation provided, is calculated by the following formula:

\[ OI = \frac{Pao₂ \times Fio₂ \times 100}{\text{mean airway pressure}} \]

For the patient in the vignette, the OI is 43.8. An OI greater than 40 is an indication for use of extracorporeal membrane oxygenation (ECMO) when all medical interventions have been maximized. Although the infant in the vignette is being supported aggressively, some might consider additional interventions. Such interventions include inhaled nitric oxide (NO), hyperventilation to induce respiratory alkalosis, pharmacologic paralysis, administration of magnesium sulfate, surfactant lavage, change of ventilator to high-frequency jet ventilation (HFJV), volume ventilation or time-cycled pressure-limited ventilation, liquid ventilation, and administration of sildenafil.

Of the additional interventions suggested for treatment of hypoxic respiratory failure due to meconium aspiration complicated by pulmonary hypertension, inhaled NO has been proven to be effective and safe for improving oxygenation and reducing the need for ECMO. Inhaled NO
can be administered easily through the ventilator circuit to reverse pulmonary hypertension selectively. NO normally is produced by pulmonary vascular endothelial cells. NO synthetase catalyzes the conversion of arginine and oxygen to citrulline and NO. NO then diffuses into the perivascular smooth muscle cell and activates guanylate cyclase to convert guanosine triphosphate into cyclic guanosine monophosphate (cGMP). cGMP produces pulmonary vascular smooth muscle relaxation, thereby improving pulmonary blood flow and reducing ventilation-perfusion mismatching. Inhalation of NO into alveoli is an alternative route for delivery to pulmonary vascular smooth muscle cells to maintain normal pulmonary vascular resistance when the endothelial NO supply is insufficient (Figure 1). Once in the smooth muscle cell, NO activates guanylate cyclase, then diffuses into the pulmonary blood vessels, where it binds with hemoglobin to form methemoglobin. Methemoglobin is reduced rapidly, yielding nontoxic nitrates that are excreted in the urine. In rare patients who have abnormal methemoglobin reductase or at high doses of inhaled NO (>20 ppm), the conversion is slow or enzyme activity is overwhelmed, and methemoglobinemia may occur. Serial methemoglobin levels should be measured to monitor this risk. The other major concern with inhaled NO is production of nitrogen dioxide and peroxynitrites because NO is a very reactive oxygen species. Continuous monitoring of nitrogen dioxide levels in exhaled gas to keep levels lower than 5 ppm and limiting the duration of inhaled NO exposure are recommended to reduce such risks.

ECMO is a proven treatment for hypoxemic respiratory failure unresponsive to maximal medical therapy. However, cardiopulmonary bypass is invasive, and the risks are greater than for a trial of inhaled NO. Hemorrhage, air emboli, thromboemboli, ischemic brain injury, hypertension, renal insufficiency, exposure to large amounts of blood, and mechanical complications may complicate the course of critically ill infants receiving cardiopulmonary bypass. Despite a higher risk for complications, outcomes for critically ill infants who are treated with or without cardiopulmonary bypass do not differ. This suggests that the underlying cause for morbidity is the illness itself and that safeguards to minimize complications of ECMO generally are successful. Although proven successful for severe meconium aspiration, ECMO is not preferred over inhaled NO administration because of the invasiveness and potential risks. Nevertheless, arrangements for ECMO should be considered in critically ill infants because the need for ECMO has been shown to be 64% to 71% in control patients compared with 40% to 46% in those receiving inhaled NO.

HFJV has not been proven effective in large, multicenter, randomized trials for treatment of severe meconium aspiration syndrome. The infant described in the vignette is critically ill and at high risk for dying from hypoxemic respiratory failure and pulmonary hypertension. During conversion from high-frequency oscillation to HFJV, pulmonary hypertension may worsen. If inhaled NO and ECMO are not available and the patient continues to deteriorate, alternative ventilation modes such as HFJV, volume ventilation, and other interventions could be considered.

Liquid ventilation devices using perfluorocarbons to carry oxygen and carbon dioxide have been successful in animal studies, but no clinical trials in human infants have demonstrated efficacy and safety in meconium aspiration syndrome. Liquid ventilation use should be limited to the context of clinical research.

Surfactant administered as a bolus has been found effective and safe in small numbers of neonates who had meconium aspiration studied in randomized trials. Surfactant lavage, however, has not been proven effective and safe in preliminary clinical trials. As with liquid ventilation, surfactant lavage for severe meconium aspiration syndrome should be used within the context of clinical research.

References:


**Content Specifications:**

- Understand the prevention and management of meconium aspiration syndrome
- Understand the indications for and techniques for administration of inhaled nitric oxide
- Understand the risks of administration of inhaled nitric oxide
- Understand the indications for and techniques of high frequency ventilation
- Understand the indications for and techniques of extracorporeal membrane oxygenation
Figure. Nitric oxide and the lung.
An 800-g newborn is delivered at 27 weeks' gestation. Her hospital course includes a requirement for supplemental oxygen until 31 weeks' postmenstrual age (PMA). At 33 weeks' PMA, she is transported from her sea-level hospital to one at an elevation of 5,000 ft. An arterial blood gas in room air right before the transport shows: pH 7.40, PaCO2 42 mmHg, and PaO2 92 mmHg (7.5 mmHg = 1 kPa). On arrival at her new hospital, another arterial blood gas shows the same pH and a PaCO2 of 40 mmHg.

Of the following, the likely PaO2 is CLOSEST to:

<table>
<thead>
<tr>
<th>Option</th>
<th>Value (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
</tr>
</tbody>
</table>

You selected 2, the correct answer is 3.

The oxygen tension in the blood (PaO2) can be calculated from the oxygen tension in the alveolus (PAO2) and the alveolar-arterial gradient (A-aDO2), which can be calculated from the first set of blood gasses in the vignette using the alveolar gas equation (Section 1). The specific calculations are reviewed below in Section 2. The calculated A-aDO2 is 7 mmHg, the calculated PAO2 at altitude is 78 mmHg, and the calculated PaO2 is 71 mmHg. The derivation of the alveolar gas equation is presented in Section 3 and is included for its own elegance; the derivation is not essential to answering the question in the vignette.

**Section 1: Alveolar Gas Equation**

The (A-aDO2) is the difference between the alveolar and arterial oxygen tensions:
\[(A-aDO_2) = (P_AO_2 - P_aO_2)\]

In healthy adults in room air, \(A-aDO_2\) is usually 10 mmHg to 20 mmHg and increases with lung disease, cardiac shunt fraction, and the fraction of inspired \(O_2\). A healthy term infant may have an \(A-aDO_2\) of 20 mmHg to 40 mmHg for several days after birth.

\(P_AO_2\) is calculated via the alveolar gas equation:

\[P_AO_2 = \text{FiO}_2 \times (Bp-47) - (P_ACO_2 / R) + [P_ACO_2 \times \text{FiO}_2 \times (1-R)/R]\]

in which \(\text{FiO}_2\) = fraction of inspired \(O_2\), \(Bp\) = barometric pressure in mmHg, 47 is the vapor pressure of water in mmHg at 37°C \(P_ACO_2\) = alveolar \(CO_2\) (estimated as equal to the blood carbon dioxide, \(PaCO_2\)), and \(R\) = respiratory quotient (rate of \(CO_2\) production / rate of \(O_2\) consumption, usually 0.8, less if there are more lipids in the diet). The derivation of the alveolar gas equation is given below in Section 3.

\(Bp\) is a complex function of altitude, temperature, and weather. For the first 10,000 ft, a good estimate of \(Bp\) can be obtained by assuming a linear decrease of 23 mmHg for every 1000 ft above sea level. Acclimatization responses in the human include hyperventilation to reduce \(P_ACO_2\), polycythemia to increase oxygen carrying capacity, and increased 2,3-diphosphoglycerate to shift the hemoglobin-\(O_2\) dissociation curve to the right, thereby facilitating oxygen delivery.

The third term in the alveolar gas equation often is ignored in practice, with little loss in accuracy, as it is usually a small number.

**Section 2: Calculations**

Using the alveolar gas equation and the blood gas values at sea level from the vignette:

Sea level \(P_AO_2\) = \((0.21 \times [760-47]) - (42 / 0.8) + (42 \times 0.21 \times [1-0.8]/0.8) = 99\) mmHg
This result and the measured $P_aO_2$ of 92 from the vignette give:

$$A-aDO_2 = 99 - 92 = 7 \text{ mmHg}$$

The $A-aDO_2$ is unlikely to change dramatically during the transport, barring a dramatic change in the child's pulmonary status.

Once at 5000 ft altitude, the Bp decrease is calculated and inserted into the alveolar gas equation:

$$\text{Altitude } P_AO_2 = 0.21 \times ([760-(23 \times 5)]-47) - (40 / 0.8) + 40 \times 0.21 \times (1-0.8)/0.8 = 78 \text{ mmHg}$$

From the definition of $A-aDO_2$:

$$A-aDO_2 = 78 - X = 7, \text{ or } X = 78 - 7 = 71 \text{ mmHg}, \text{ closest to the preferred answer.}$$

**Section 3: Derivation of the Alveolar Gas Equation**

The derivation of the alveolar gas equation begins with the definition of the respiratory quotient:

$$R = V_{dot}CO_2 / V_{dot}O_2$$

The $V_{dot}$ notation indicates a rate of change in volume, so that $V_{dot}O_2$ is the rate of $O_2$ consumption, and $V_{dot}CO_2$ is the rate of $CO_2$ production. $V_{dot_{AE}}$ can be used to signify the rate of total alveolar gas exhalation, and $V_{dot_{AI}}$ can be the rate of total alveolar gas inhalation. The fraction of each gas component in the inhaled, exhaled, or total alveolar gas is signified by the $F$ notation. Then, the rate of $O_2$ consumed equals the rate of $O_2$ inhaled minus the rate of $O_2$ exhaled, or:

$$V_{dot}O_2 = (V_{dot_{AI}} \times FiO_2) - (V_{dot_{AE}} \times F_AO_2)$$
The rate of CO₂ inhalation is negligible, so the rate of CO₂ exhalation is:

\[ V_{\text{dotCO}_2} = V_{\text{dotAE}} \times F_A \text{CO}_2 \]

Substituting the Vdot expressions in the definition of R and rearranging gives the expanded definition of R:

\[ R = F_A \text{CO}_2 / [F_{\text{I}_O}_2 \times (V_{\text{dotAI}} / V_{\text{dotAE}}) - F_A \text{O}_2] \]

The ratio of inhaled to exhaled alveolar ventilations \( V_{\text{dotAI}} / V_{\text{dotAE}} \) can be found using the fact that the inhaled nitrogen (N₂) is the same as the exhaled.

The rate of N₂ inhalation is \( V_{\text{dotAI}} \times (1-F_{\text{I}_O}_2) \). Since CO₂ is a significant part of the exhaled gas, the rate of N₂ exhalation includes a CO₂ factor: \( V_{\text{dotAE}} \times (1-F_{A\text{O}_2} - F_A \text{CO}_2) \). Setting these two terms equal to each other and solving for \( (V_{\text{dotAI}} / V_{\text{dotAE}}) \):

\[ (V_{\text{dotAI}} / V_{\text{dotAE}}) = (1-F_{A\text{O}_2} - F_A \text{CO}_2) / (1-F_{\text{I}_O}_2) \]

Substituting this in the expanded definition of R above:

\[ R = F_A \text{CO}_2 / (F_{\text{I}_O}_2 \times [(1-F_{A\text{O}_2} - F_A \text{CO}_2) / (1-F_{\text{I}_O}_2)] - F_A \text{O}_2) \]

Solving for \( F_A \text{O}_2 \) gives:

\[ F_A \text{O}_2 = F_{\text{I}_O}_2 - (F_A \text{CO}_2 / R) + [F_A \text{CO}_2 \times F_{\text{I}_O}_2 \times (1-R)/R] \]

For each gas, the partial pressure from the fractional concentration, \( P_{\text{gas}} = F_{\text{gas}} \times (Bp-47) \), allowing the conversion to partial pressures by multiplying each term of the above equation by \( (Bp - 47) \):

\[ F_A \text{O}_2 \times (Bp-47) = F_{\text{I}_O}_2 \times (Bp-47) - [F_A \text{CO}_2 \times (Bp -47)/R] + [F_A \text{CO}_2 \times (Bp-47) \times F_{\text{I}_O}_2 \times (1-R)/R] \]

or:

\[ F_A \text{O}_2 \times (Bp-47) = F_{\text{I}_O}_2 \times (Bp-47) - [F_A \text{CO}_2 \times (Bp -47)/R] + [F_A \text{CO}_2 \times (Bp-47) \times F_{\text{I}_O}_2 \times (1-R)/R] \]
\[ P_{A\text{O}_2} = \text{FiO}_2 \times (Bp-47) - \frac{(P_{A\text{CO}_2} \times \text{FiO}_2)}{R} + \left[ \frac{P_{A\text{CO}_2} \times \text{FiO}_2 \times (1-R)}{R} \right], \text{the alveolar gas equation}. \]

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


Content Specification(s):

Know how to calculate an alveolar-arterial gradient
You are helping treat a male infant of 25 weeks' gestation who is now 79 days old. The infant was given surfactant after his birth and weaned from mechanical ventilation to continuous positive airway pressure 15 hours after birth. At 7 days of age, mechanical ventilation was required again for increasing respiratory distress and cyanosis. He continues to receive mechanical ventilation and supplemental oxygen (Fio₂, approximately 0.35) and is growing regularly with enteral feedings. The Figure depicts the infant's chest radiograph. The infant's parents ask you to describe the abnormalities present in the lungs of their son.

**Figure: Chest Radiograph**

Of the following, the PREDOMINANT finding that would be seen microscopically is:

1. airway and alveolar fibrosis
2. airway necrosis and obstruction
3. alveolar hypoplasia
4. bronchiolar and alveolar destruction
5. bronchiolar metaplasia and hyperplasia

You selected 3, the correct answer is 2.

The infant in the vignette has bronchopulmonary dysplasia (BPD), the most common chronic respiratory disease of childhood. He has severe BPD because he continues to require mechanical ventilation beyond 36 weeks' postmenstrual age.
Table 1. Definition of BPD: Diagnostic Criteria

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Time of Assessment</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;32 weeks</td>
<td>36 weeks PMA or discharge to home*; treatment with oxygen (Fio2 &gt; 0.21) for at least 28 days PLUS</td>
<td>Breathing room air at 36 weeks PMA or discharge*</td>
<td>Breathing Fio2 0.22-0.30 at 36 weeks PMA or discharge*</td>
<td>Breathing Fio2 &gt; 0.30 +/- positive pressure ventilation or continuous positive airway pressure at 36 weeks PMA or discharge*</td>
</tr>
<tr>
<td>≥32 weeks</td>
<td>28-56 days postnatal age or discharge to home*; treatment with oxygen (Fio2 &gt; 0.21) for at least 28 days PLUS</td>
<td>Breathing room air by 56 days postnatal age or discharge*</td>
<td>Breathing Fio2 0.22-0.30 at 56 days postnatal age or discharge*</td>
<td>Breathing Fio2 &gt; 0.30 +/- positive pressure ventilation or continuous positive airway pressure at 56 days postnatal age or discharge*</td>
</tr>
</tbody>
</table>

BPD = bronchopulmonary dysplasia; Fio2 = fraction of inspired oxygen; PMA = postmenstrual age.

* Whichever came first.

The pathobiology of BPD has changed with better understanding of this disorder and advances in the care of extremely preterm infants. The original description of BPD included preterm infants predominantly at 30 to 34 weeks' gestation with severe respiratory distress syndrome that required support with high concentrations of oxygen and mechanical ventilation. These infants were not exposed to antenatal steroids and did not receive the benefits of surfactant replacement.

Infants with the "new BPD" are most often born extremely preterm and have mild respiratory distress syndrome due to increased use of antenatal steroids and postnatal surfactant administration. Often progressive respiratory distress recurs or apnea becomes frequent or severe requiring mechanical ventilation several days to weeks after birth. This progression to symptomatic BPD is a complex developmental and reparative response of the immature lung to many different pathogenic factors. Such factors may include a genetic predisposition (family history of asthma, genetic polymorphisms for factors important in lung development such as fibroblast growth factor 10, transforming growth factor beta), antenatal steroids, inflammation (such as antenatal chorioamnionitis, postnatal pneumonia, and sepsis), oxygen toxicity, mechanical ventilation, pulmonary edema (patent ductus arteriosus, excess fluid load), and nutritional deficiencies (vitamin A, vitamin E).

The characteristic pathologic feature of the "new BPD" is alveolar hypoplasia, with fewer and larger alveoli and decreased pulmonary microvascular development. The airways and alveoli of these lungs have less fibrosis, epithelial metaplasia and hyperplasia, airway necrosis and obstruction with inflammatory exudate,
bronchiolar and alveolar destruction, and smooth muscle hypertrophy than found with the originally described BPD in more mature preterm infants. In "new BPD," the lungs are also more uniformly inflated. Interstitial edema and smooth muscle hypertrophy of pulmonary arterioles may be present in severe BPD, whether "new" or as originally described.

Alveolization begins during the late canalicular and early saccular stages of fetal lung development and is completed by about 18 months after birth, with most alveolization occurring by 5 to 6 months of age in a term infant. Postnatal lung alveolization in extremely preterm infants is complex because many interrelated events that are necessary for normal development are altered by antenatal and postnatal factors (Table 2).

Table 2. Examples of Factors Affecting Alveolization

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular endothelial growth factor</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Neuropilins</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Platelet-derived growth factor A</td>
<td>Positive pressure ventilation</td>
</tr>
<tr>
<td>Retinoic acid</td>
<td></td>
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<tr>
<td>Estrogen</td>
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<tr>
<td>Thyroid hormone</td>
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<tr>
<td>Fibroblast growth factor</td>
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<tr>
<td>Nutrition</td>
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Chorioamnionitis and associated inflammatory cytokines and mediators have been found to impair alveolization. Alveolar size and volume are increased but fewer alveoli are present in preterm lambs exposed to endotoxin, an inflammatory mediator associated with some microorganisms that cause chorioamnionitis. Similarly, antenatal betamethasone administered to preterm lambs also caused increases alveolar size and decreased alveolar number. If this negative effect is also present in human infants, use of antenatal betamethasone must be balanced against the beneficial impact on lung parenchyma maturation, surfactant production, lung compliance, vascular permeability, and lung water clearance. The stimulatory and inhibitory effects of betamethasone on lung development demonstrate the complex interplay and balance of molecular control mechanisms, cell proliferation, and pulmonary microvascular development.

Postnatal lung morphogenesis may be impeded by life support interventions and complications of preterm birth. High concentrations of oxygen, positive pressure ventilation, pneumonia, and associated pulmonary inflammatory responses impair alveolization, damage tissues, and stimulate immature repair processes. These effects may be amplified in the preterm lung primed for an inflammatory reaction because of colonization by organisms acquired in utero or predisposing genetic polymorphisms in infants who are susceptible to lung injury. Postnatal corticosteroids and nutritional deficiencies, especially vitamin A deficiency, also negatively affect alveolization. Pulmonary development in preterm infants, like other developmental processes, requires complex interactions that normally are tightly controlled. Preterm birth, pathophysiologic insults, and reparative processes disrupt these interactions. The balance of these factors determines the severity of BPD.

References:


Husain AN, Siddiqui NH, Stocker JT. Pathology of arrested acinar development of postsurfactant bronchopulmonary dysplasia. Pathology. 1998;29:710-717


**American Board of Pediatrics Content Specification(s):**

Understand the pathogenesis and pathophysiology of bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD)

Recognize the clinical features of BPD/CLD

Recognize the radiographic features of BPD

Recognize the pathologic features of BPD/CLD
You are managing an 11-day-old, 35-week-gestation female infant who is recovering from hyaline membrane disease. She was treated with surfactant, high-frequency ventilation, and inhaled nitric oxide. The infant had been receiving low oxygen and ventilator support until this morning when she became mottled, poorly perfused, and required substantial increases in support to maintain acceptable gas exchange. A chest radiograph shows left lower and left upper lobe infiltrates that were not present on the previous chest film.

Of the following, the MOST accurate statement about the immunologic pulmonary defense mechanisms in this infant is that:

1. Complement plays a minor role in the innate immune response.
2. Nitric oxide synthesis is downregulated by microbial cell products and cytokines.
3. Pattern recognition receptors are absent on soluble elements of the innate immune response.
4. Surfactant protein A solely functions to support pulmonary mechanics.
5. Surfactant protein D augments pulmonary immune function.

You selected 2, the correct answer is 5.

Pneumonia is a significant cause for morbidity and mortality in newborn infants. The course of more than 10% of infants in neonatal intensive care units is complicated by pneumonia, and the mortality rate may be as high as 20%. Pneumonia may be acquired in utero by transplacental spread through the umbilical cord and aspiration of microorganisms within the amniotic fluid. Postnatal acquisition occurs by spread from the blood stream or aspiration during or following birth.

Pulmonary host defense mechanisms are broadly defined as either mechanical or immunologic. Mechanical barriers include the larynx and pharynx, mucus, and mucociliary clearance mechanisms such as the cough reflex. The mechanical defenses filter about 99% of inhaled particles and microorganisms, thereby reducing antigen exposure and activation of the host immune responses. Immunologic host defenses are either innate and nonspecific or adaptive and specific. Innate immune mechanisms include macrophages, cytokines, chemotaxins, granulocytes, and natural killer cells (Figure).

Figure. Innate Immunity in the Lung with Cellular (Alveolar Macrophages,
Adaptive host defenses are characterized by immunologic memory and long-term cell-mediated and humoral immune systems that include antigen-presenting cells, T cells, B cells, and immunoglobulins.

Newborn infants are immunologically naïve. Although this is true for all newborn infants, premature infants are especially compromised due to immature defense mechanisms. Thus, the response to infection by newborn infants is largely dependent on innate, nonspecific, and quickly recruitable host defenses rather than on the adaptive, specific defenses that require time to develop pools of lymphocytes and antibodies that are specific to the inciting antigenic stimulus.

The innate host defenses, both cellular and secreted/soluble elements, recognize structurally conserved molecular sequences that are shared among groups of pathogens. These sequences are called "pathogen-associated molecular patterns" (PAMPS) and include lipopolysaccharides (gram-negative bacteria), lipoteichoic acids (gram-positive bacteria), bacterial lipoproteins or peptidoglycans, mycobacterial glycolipids, fungal mannans, bacterial DNA sequences, and double-stranded RNAs. PAMPS are recognized by "pattern recognition receptors" (PRRs) present on cellular elements (such as phagocytes and epithelial and endothelial "barrier" defense cells), and soluble or secreted elements (such as complement, fibronectin, defensins, cathelicidins, lysozyme, collectins, and nitric oxide). PRRs are germline encoded and do not depend on clonal expansion and development of immunologic memory.

The innate immune response includes a number of soluble components, many of which are found in the fluid lining the airways of the lung (Figure). Examples include complement, surfactant proteins, nitric oxide (NO), fibronectin, iron-binding proteins, antimicrobial peptides, lipopolysaccharide-binding protein, and carbon monoxide. These soluble or secreted elements in the airway lining fluid serve to bind and attack pathogens, act as chemoattractants for phagocytic cells, modulate the immune response, and complement the physical barriers provided by mucus and mucociliary clearance.

Complement is a major component of the innate immune response. In addition to
direct bacterial lysis, complement serves as an important opsonin and chemoattractant. Immunoglobulins G and M bind and activate complement factor C1q, which sets in motion the classic cascade of complement proteins (classic pathway). Mannin-binding lectin (MBL) recognizes and binds bacterial, fungal, mycobacterial, and some viral proteins. This interaction activates complement factor 4 and the subsequent cascade (MBL pathway). Endotoxin, polysaccharides, immune complexes, and some bacterial and fungal surface components initiate the complement cascade by binding circulating complement factor C3b fragments and, through a series of steps including C3bBb binding, alternative pathway "C3/C5" convertase induction, C5a and C5b formation, activate the terminal components of the complement system to form C5b-9 (alternative pathway). C5b-9, the common product of each of the complement pathways, disrupts lipid-bilayers in cell membranes by formation of pores that allow cytotoxic fluid and solute shifts to occur. Complement is found throughout the lung. It is derived from the blood but is also produced by alveolar macrophages, pulmonary fibroblasts, and type II epithelial cells. Complement activity of all three pathways is diminished in preterm infants. In term infants, as is likely in the infant in this vignette, the alternative pathway is relatively impaired; the classic and MBL pathways, however, function as in adults.

Collectins, or collagenous c-type lectins, are carbohydrate-binding proteins that bind microbial carbohydrate and glycolipid PAMPs. They modulate the inflammatory response by being a chemoattractant and stimulating the respiratory burst and cytokine secretion by macrophages when pathogenic organisms are present within the lung. In addition, collectins inhibit T-cell proliferation when no infection or inflammation is present, thereby dampening and, perhaps, localizing the inflammatory response. Surfactant protein A (SPA) and D (SPD) are pulmonary collectins that have these immune functions in addition to their roles in pulmonary mechanics. Both SPA and SPD synthesis by type II cells is inducible in response to acute lung injury and pathogen exposure. Therefore, SPA and SPD protect the lung by supporting pulmonary function, augmenting immune function during infection and dampening inflammatory reactions when no infection or lung injury is present.

Nitric oxide is produced constitutively by vascular endothelium, neutrophils, platelets, and neurons. Synthesis of NO can also be induced in vascular smooth muscle cells, mononuclear phagocytes, epithelial cells, and hepatocytes. It is known best as a vasodilator, smooth muscle relaxant, and platelet inhibitor in the lung. During infections, NO synthesis can be upregulated by microbial cell products and cytokines. Nitrosylated thiols produced within NO metabolic pathways may be bacteriostatic or bacteriocidal depending on the organism. Nitric oxide also disrupts DNAs, inhibits RNA synthesis, and damages biomembranes by lipid peroxidation. Furthermore, NO enhances macrophage motility, upregulates complement and Fc receptors on phagocytes, augments the respiratory burst and peroxynitrite formation, and improves mucociliary clearance to improve phagocyte movement to sites of infection, microbial killing, and microbial clearance from the lung.

A number of other soluble molecules constitute the innate immune response to infection, especially within the lung. Fibronectin is synthesized by hepatocytes but also by bronchoepithelial cells and alveolar macrophages. It functions as an opsonin and chemoattractant, and adheres to vessel walls in leukocytes.

Iron-binding proteins, such as lactoferrin, are found in higher concentrations in the lung than serum. They bind elemental iron and inhibit microbial growth. Iron-binding proteins also attach to the lipopolysaccharides of gram-negative bacteria and some viruses (such as cytomegalovirus and human immunodeficiency virus). Bacterial "twitching" occurs when iron-binding proteins attach and this suppresses biofilm production, thereby exposing microbes to other immune effector molecules and cells.

Antimicrobial peptides such as defensins, cathelicidins, and lysozyme are produced by airway epithelium, neutrophils, natural killer cells, monocytes, and lymphocytes. These peptides disrupt cell membranes of a broad, but specific, range of bacteria, fungi, and viruses. The specificity of each of these antimicrobial peptides speaks to the need for many different peptides to provide an innate immune response. Lipopolysaccharide-binding protein is a normal constituent of lung fluid and, although primarily produced by hepatocytes, can be produced by type II cells and alveolar macrophages in the lung when stimulated by pathogens and inflammatory mediators. It binds and disaggregates endotoxin and stimulates ingestion by macrophages and monocytes that, in turn, are induced to secrete "early response" mediators such as tumor necrosis factor alpha and interleukin-1 beta.

References:


American Board of Pediatrics Content Specification(s):

Understand the role of fibronectin in host defense
Understand the role of lactoferrin in host defense
Understand what cytokines regulate immune function
Know that cytokines regulate phagocyte development and function
A female infant of 33 weeks gestational age develops tachypnea and retractions shortly after birth. The delivery was atraumatic. A chest radiograph is obtained (Figure 1).

The infant's respiratory distress worsens and a left-sided thoracocentesis is performed. Approximately 50 mL of clear fluid is removed. Analysis of the pleural fluid reveals a white blood cell count of $3.5 \times 10^3/\mu L$ ($3.5 \times 10^9/L$) with 95% lymphocytes. During your discussion of congenital chylothorax with the medical students, you ask about the anatomy of the thoracic duct.

Of the following, the MOST likely site at which the thoracic duct drains lymph into the venous system is the junction of the:

1. left brachiocephalic vein and the superior vena cava
2. left internal jugular vein and the left subclavian vein
3. left internal jugular vein and the right subclavian vein
4. left internal jugular vein and the external jugular vein
5. superior vena cava and right atrium

You selected 2, the correct answer is 2.

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Chylothorax is the presence of lymphatic fluid in the pleural space secondary to leakage from the thoracic duct, the right lymphatic duct, or one of their tributaries. A chylothorax in a newborn is due to either a congenital malformation of the lymphatic system or birth trauma. Congenital chylothorax has been associated
with Turner syndrome, Down syndrome, and Noonan syndrome.

Pleural fluid obtained by thoracocentesis shortly after birth will be clear and will become opalescent after the introduction of milk feedings. Elevated triglyceride levels (>110 mg/dL [>1.2 mmol/L]) in the pleural fluid following feedings reflects a 99% chance that the fluid is chyle.

One of the important roles of the lymphatic system is to drain surplus interstitial fluid and leaked plasma proteins back into the bloodstream. Edema develops when the rate of transvascular fluid filtration from the microcirculation exceeds the rate of fluid clearance from the interstitial space by the lymphatics.

Lymphatic capillaries end bluntly in loose connective tissue. The smallest terminal lymphatic capillaries are similar to blood capillaries in that there is no smooth muscle around the endothelium. As the lymphatics are traced centrally, smooth muscle cells and valves appear. Lymphatic valves provide directionality to lymph flow. Unlike the circulatory system, the lymphatic system lacks a pump to move the fluid. Lymph is propelled centrally by lymph vessel contraction, respiratory motion, and muscle movement. Inactivity results in lymphedema accumulation.

The lymphatic system begins to develop in the embryo at the end of the sixth week, in close association with the venous system. Six primary lymph sacs develop by the ninth week and later become interconnected by lymphatic vessels. Abnormal development of lymphatic connections may result in congenital chylothorax or a cystic hygroma.

The right lymphatic duct drains lymph from the right arm and from the right side of the head, neck, and thorax (Figure 2).

**Figure 2**

The right lymphatic duct drains into the bloodstream at the junction of the right internal jugular and right subclavian veins.

The thoracic duct drains lymph from the remainder of the body. The thoracic duct
begins in the abdomen as an egg-shaped dilatation called the cisterna chyli, which is located anterior to the second lumbar vertebra (Figure 3).

The thoracic duct ascends anterior to the vertebral bodies, usually on the right side, and enters the thorax through the aortic hiatus of the diaphragm. At the fourth or fifth thoracic vertebra, the thoracic duct crosses toward the left side and ascends behind the aortic arch. As the thoracic duct ascends into the neck, it forms an arch that rises above the clavicle. The thoracic duct drains lymph into the venous system at the junction of the left internal jugular vein and left subclavian vein (Figure 2).
The course of the thoracic duct subjects it to injury during abdominal, thoracic, or neck procedures.

Although most of the lymph drains into the venous system through either the right lymphatic duct or the thoracic duct, lymphatic vessels communicate with veins in many other parts of the body. Thus, ligation of a major lymphatic duct such as the thoracic duct usually has a transient effect on lymph drainage until peripheral lymphaticovenous drainage systems are established.

Most cases of congenital chylothorax can be managed by drainage of the pleural fluid with repeated thoracocentesis or continuous drainage by a chest tube. The fluid of a chylothorax may be so rich in lymphocytes and protein that prolonged drainage results in lymphopenia and hypoproteinemia with an increased risk of infection and edema. Initially, feedings are withheld and nutritional support is provided by total parenteral nutrition. Utilization of a formula rich in medium-chain triglycerides on initiation of feedings is often recommended. Infants with intractable chylothorax have been successfully treated with octreotide, which reduces intestinal absorption of triglycerides and decreases chyle production.

Diagram courtesy of William Wassom

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References:


American Board of Pediatrics Content Specification(s):

Understand the pathophysiology and recognize the clinical, radiographic, and laboratory manifestations of hydrothorax/chylothorax

Plan the therapeutic management of hydrothorax/chylothorax
You are reviewing the chest radiograph of a male infant born at 34 weeks' gestation who presents at 2 days of age with severe respiratory failure complicated by persistent pulmonary hypertension (Figure 1).

**Figure 1. Chest Radiograph**

The infant is being treated with antibiotics, dopamine, mechanical ventilation fraction of inspired oxygen \([\text{FiO}_2]\) 1.0, and inhaled nitric oxide. His white blood cell count is \(1.2 \times 10^3/\mu\text{L} (1.2 \times 10^9/\text{L})\) with 21% bands and 60% neutrophils. His mother's perinatal history is significant for recurrent urinary tract infections with *Escherichia coli*. You are discussing the infant's pulmonary host defense mechanisms at the bedside with his parents and pediatric residents.

Of the following, the MOST accurate statement about the infant's ability to mount a pulmonary immune response is that:

1. Gas flow turbulence is an important mechanism for deposition of organisms in mucus of the upper and lower airways.
2. Inhaled nitric oxide decreases ciliary motility and increases mucus fluidity.
3. Laryngeal elevation and forward movement increase the risk for aspiration of microorganisms and oropharyngeal fluid during swallowing.
4. Mucociliary clearance in neonates is rapid because of increased periciliary fluid levels.
5. Mucociliary function is enhanced during inflammation.

You selected 2, the correct answer is 1.

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Pneumonia is a significant cause for morbidity and mortality in newborn infants.
The clinical course of more than 10% of infants in neonatal intensive care units is complicated by pneumonia, and the associated mortality rate may be as high as 20%. Pneumonia may be acquired in utero by transplacental spread through the umbilical cord and aspiration of microorganisms in the amniotic fluid. Postnatal acquisition occurs by spread from the bloodstream or aspiration during or following birth.

Three pathologic forms of pneumonia have been described and are characterized by hyaline membrane formation, suppurative inflammation, or interstitial pneumonitis. Hyaline membrane formation is a nonspecific response to lung injury and occurs during pneumonia when alveolar epithelial injury and necrotic cell components inhibit surfactant activity. Atelectasis, both diffuse, as in respiratory distress syndrome, and focal, causes a decrease in functional residual capacity and compliance and increase in intrapulmonary shunt. Suppurative pneumonias caused by enteric bacilli, Staphylococcus aureus, and fungi are associated with an intense inflammatory response. Necrosis, microabscess formation, and obstruction of terminal bronchioles with microorganisms and cellular debris contribute to poor pulmonary function and hypoxemia. Interstitial pneumonia most often results from viral invasion of the pulmonary interstitium. Interstitial inflammation, edema, mononuclear infiltration, septal hyperplasia, and necrosis characterize this type of pneumonia. Alveoli are generally spared, although hemorrhage, inflammatory exudates, and cell debris may be associated with hyaline membrane formation.

Pulmonary host defense mechanisms are broadly defined as either mechanical or immunologic. Mechanical barriers include the larynx and pharynx, mucus, and mucociliary clearance mechanisms such as the cough reflex. The mechanical defenses filter about 99% of inhaled particles and microorganisms thereby reducing antigen exposure and activation of the host immune responses. Immunologic host defenses are either innate and nonspecific or adaptive and specific. Innate immune mechanisms include macrophages, cytokines, chemotaxins, granulocytes, and natural killer cells. Adaptive host defenses are characterized by immunologic memory and long-term cell-mediated and humoral immune systems that include antigen-presenting cells, T cells, B cells, and immunoglobulins.

Neonates are predominantly nasal breathers. Nasal hairs and turbinates filter particles as small as 10 μm. These structures cause turbulent flow in the upper airway thereby increasing contact and deposition of inhaled particles on the epithelial mucus layer. In the lower airway, airway bifurcations also induce gas flow turbulence and can enhance deposition of particles by 100-fold.

Epithelial cell integrity, mucociliary function, and integrated airway reflexes are critical to prevent bacterial colonization and invasion. The neonate is prone to infection because mucociliary function and airway reflexes are immature during the first weeks after birth. Furthermore, airway epithelium may be disrupted by exposure to mechanical devices (such as endotracheal tubes, suction catheters, or caustic medications), high concentrations of oxygen, dry gas, mechanical ventilation, toxins produced by microorganisms, and inflammatory cytokines and mediators.

The airway epithelium serves to prevent passage of microorganisms into the interstitium of the lung and, most importantly, functions to carry them out of the lung. The apical tight-junctions of airway epithelial cells, periciliary fluid, and mucus overlying cilia provide physical barriers to microorganisms (Figure 2).

Figure 2. Airway Epithelial Cell and Mucociliary Structure
Ciliated columnar epithelial cells dominate the trachea and large airways in the form of a continuous layer, or carpet, of cells. In the smaller airways and terminal bronchioles, ciliated cuboidal epithelial cells predominate. Serous cells and goblet cells responsible for serous fluid and mucus production, respectively, are both found in the trachea and upper airways. Clara cells that produce watery secretions are found only in the smaller airways where movement of more viscous mucus would be difficult.

Cilia function to expel microorganisms out of the lung. This expulsion occurs because ciliary beat frequency and ciliary vertical lift motion act to move and mix microorganisms in the overlying mucus layer. These movements are enhanced by warm temperature, nitric oxide (endogenous and inhaled), beta-adrenergic agonists, cyclic adenosine monophosphate-dependant kinase, activation of G protein-coupled purinoreceptors, and adenosine released by nucleotide-hydrolyzing enzymes. In contrast, agents that inhibit ciliary function (beat slowing, beat disorientation, ciliostasis, cell death) include high oxygen concentrations, bacterial toxins, inflammatory mediators (such as prostaglandins, leukotrienes, platelet-activating factor, tumor necrosis factor alpha, interleukin 9), dry gases, cold temperature, and anesthetic gases. Pathogenic bacteria reduce mucociliary function by decreasing ciliary beat frequency and increasing both periciliary fluid levels and mucus production. Overall, mucociliary function is impaired during infection and inflammation.

The thin, nonviscous fluid that bathes the cilia and lies between the epithelial cell surface and mucus layer is called the periciliary fluid (Figure 2).

**Figure 2. Airway Epithelial Cell and Mucociliary Structure**

The level of this fluid determines whether the tips of the cilia adequately engage
the overlying mucus or whether the mucus and epithelial glycocalyx layer come in contact. If the periciliary fluid level is too high, the mucus layer and tips of the cilia do not have adequate surface contact to generate movement. If the periciliary fluid level is too low, the mucus and epithelial glycocalyx layers merge and surround the cilia with a viscous fluid that impedes movement. Periciliary fluid secretion is regulated by an active transport mechanism across the epithelial cell. In neonates, a transition is occurring in periciliary fluid secretion by airway epithelial cells in the trachea and large airways from active chloride secretion and production of a thin, nonviscous fluid, to active sodium absorption and production of mucus. During this transition, newborns produce excess periciliary fluid that impedes ciliary tip contact with mucus, which is sparse because of limited production. Thus, newborns do not have optimal amounts of mucus to trap microorganisms and have impaired ability to expel the mucus.

Airway reflexes also are important barriers to aspiration of pathogenic microorganisms. In neonates, nasal breathing generates turbulent gas flow during passage through the nasal hairs and turbinates. The more cephalad position of the larynx than in the adult also allows closer approximation of the epiglottis to the soft palate to effectively isolate the upper airway from the oral cavity. During the pharyngeal stage of swallowing, the airway is also protected by elevation and forward movement of the larynx, the epiglottis overlying the laryngeal opening and sealed by contraction of the laryngeal adductor muscles, and cessation of breathing. Newborn infants have less mature integration of this protective mechanism and may have exaggerated apneic responses. The cough response is another protective reflex to limit aspiration of microorganisms. A mature cough response is found in only 50% of term infants and fewer than 25% of preterm infants. The cough response replaces the reflex laryngeal closure response and apnea response as maturation occurs. Furthermore, the compliant chest wall and trachea of the neonate limit generation of adequate shear force to overcome mucus viscosity and gravity to move mucus out of the lung.

Do you want to add anything to your Learning Plan?
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References:


American Board of Pediatrics Content Specification(s):

Understand the causes and differential diagnosis of pneumonia

Understand the clinical and laboratory features of pneumonia
An Rh-negative woman who had a high titer of antibodies to Rh(D) due to sensitization during a previous pregnancy is carrying an Rh-positive fetus. At 25 weeks' gestation, the fundal height was noted to be advanced for gestation, and there was a persistent fetal tachycardia. Early signs of hydrops were detected by ultrasonographic examination. Percutaneous umbilical blood sampling revealed a hemoglobin concentration of 4.5 g/dL. The obstetrician elected to transfuse the infant with Rh-negative red blood cells. Transfusions were accomplished successfully on two occasions. Because the donor blood provided adult hemoglobin to the fetus, the neonatologist undertook a review of the factors associated with placental oxygen transfer.

Of the following, the MOST accurate statement about transplacental respiration is:

1. Diffusion distance for gas exchange is smaller in the placenta than it is in the lung after birth.
2. Fetal hemoglobin unloads oxygen to tissues more readily than adult hemoglobin when oxygen tensions are low.
3. Oxygen saturation in the umbilical vein is normally 86% to 92% of the uterine arterial oxygen saturation.
4. Total surface area for gas exchange in the placenta is far less than in the adult lung.
5. Uterine blood supply to the placenta is autoregulated and increases as fetal demand increases.

You selected 3, the correct answer is 4.

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It is a wonder that the fetus can survive and grow at all, considering the apparent inefficiency of placental gas exchange. The human placenta is hemochorial, meaning that fetal chorionic villi, which are covered by the chorionic membrane and contain capillaries, are bathed directly in maternal oxygenated blood. However, the diffusion distance for gas exchange is seven times greater than in the lung (3.5 μm vs. 0.5 μm). The total respiratory surface of the placenta at term is 16 m² versus 50 to 60 m² for the adult lung. The lung of the term newborn has about one-sixth of the alveoli found in adult lungs. Therefore, the surface area for gas exchange in the term placenta is greater than that of the newborn lung, but far less than that of an adult. In toto, gas exchange is relatively inefficient before birth compared to afterward.

Fetal hemoglobin has a higher affinity for oxygen than adult hemoglobin at all partial pressures of oxygen in the physiologic range (http://www.answers.com/topic/fetal-hemoglobin). This is related to the fact that fetal hemoglobin does not have binding sites for 2,3-diphosphoglycerate (2,3-DPG). The 2,3-DPG binds to and stabilizes adult deoxyhemoglobin and reduces the affinity of adult hemoglobin for oxygen. Therefore,
at the tissue level, with partial pressures of oxygen between 10 mmHg and 20 mmHg (1.33 to 2.67 kPa), fetal hemoglobin unloads oxygen less efficiently than adult hemoglobin. The difference in oxygen affinity between adult and fetal hemoglobin facilitates the transfer of oxygen from maternal to fetal blood, but its existence is not absolutely essential to survival. Fetuses with almost all of their circulating hemoglobin replaced with adult hemoglobin have been able to grow in utero and to survive without permanent injury. However, they do tend to have a larger base deficit at birth.

In the placenta, the oxygen dissociation curves for both fetal and maternal (adult) hemoglobin are a bit more complicated due to a double Bohr Effect. The Bohr Effect is the tendency for hemoglobin to bind oxygen less efficiently as pH decreases. This phenomenon occurs at the capillary level and converts the oxygen dissociation curve for hemoglobin from an S-shaped single line to an S-shaped hysteresis loop with slightly different curves, depending on whether oxygen is loading in the lung or unloading to the tissues. With placental gas exchange, the pH of the fetal blood rises as CO₂ shifts to the maternal circulation. The oxygen dissociation curve for fetal hemoglobin shifts to the left (away from the adult hemoglobin curve). This increases the efficiency of the gas exchange by allowing more oxygen to load onto fetal hemoglobin at relatively low oxygen tensions. At the same time, maternal blood is taking on CO₂, which facilitates the unloading of oxygen. The two loops, however, do not overlap (see an illustration of the double Bohr Effect at http://www.anaesthesiamcq.com/downloads/placenta.pdf).

The P₅₀ (the oxygen tension at which hemoglobin is 50% saturated) of fetal hemoglobin is about 19 mmHg (2.53 kPa), significantly lower than that of adult hemoglobin (P₅₀ = 26.6 mmHg [3.55 kPa]). Umbilical arterial blood has a PO₂ in the range of 18 mmHg (2.4 kPa) (oxygen saturation [SO₂] of 45%). Passage through the placenta increases the partial pressure only to 28 mmHg (3.73 kPa) (SO₂ of 70%). Once the hemoglobin of the fetus exceeds 16.6 g/dL, cyanosis would be evident in utero. Maternal arterial blood has a PO₂ of approximately 100 mmHg (13.3 kPa) (SO₂ of 98%). Therefore, oxygen saturation in the umbilical vein is only 70% of that in the uterine artery.

Placental blood flow is not autoregulated; it is dependent on vascular pressures. Maternal hypotension or increases in placental vascular resistance (as might be seen in pre-eclampsia) are threats to fetal oxygenation.

Do you want to add anything to your Learning Plan?  
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References:


Saunders; 2004:111-122


**Content specification(s):**

Know the role of the placenta in gas exchange and oxygenation of the fetus
You are managing an 11-day-old, 41-week-gestation female infant who is recovering from meconium aspiration syndrome. She was treated with extracorporeal life support after failing to improve with high-frequency ventilation and inhaled nitric oxide. The infant had been receiving low oxygen and ventilator support until this morning when she became mottled, poorly perfused, and required substantial increases in support to maintain acceptable gas exchange. A chest radiograph shows right middle, right lower, and left upper lobe infiltrates that were not present on the previous chest film.

Of the following, the MOST accurate statement about the immunologic pulmonary defense mechanisms in this infant is that:

1. Adaptive host defense mechanisms are rapidly responsive to pathogens.
2. Alveolar macrophages recognize pathogen-associated molecular patterns.
3. Dendritic cells primarily function as phagocytes.
4. Individual toll-like receptors recognize a large spectrum of pathogens.
5. Lungs are a minor reservoir of polymorphonuclear leukocytes in neonates.

You selected [1], the correct answer is [2].

Pneumonia is a significant cause for morbidity and mortality in newborn infants. The course of more than 10% of infants in neonatal intensive care units is complicated by pneumonia, and the mortality rate may be as high as 20%. Pneumonia may be acquired in utero by transplacental spread through the umbilical cord and aspiration of microorganisms within the amniotic fluid. Postnatal acquisition occurs by spread from the blood stream or aspiration during or following birth.

Pulmonary host defense mechanisms are broadly defined as either mechanical or immunologic. Mechanical barriers include the larynx and pharynx, mucus, and mucociliary clearance mechanisms such as the cough reflex. The mechanical defenses filter about 99% of inhaled particles and microorganisms, thereby reducing antigen exposure and activation of the host immune responses. Immunologic host defenses are either innate and nonspecific or adaptive and specific. Innate immune mechanisms include macrophages, cytokines, chemotaxins, granulocytes, and natural killer cells. (Figure)

Figure. Innate Immunity in the Lung with Cellular (Alveolar Macrophages, Polymorphonuclear Leukocytes), Soluble or Secreted Components (Opsonins) and Chemoattractants
Adaptive host defenses are characterized by immunologic memory and long-term cell-mediated and humoral immune systems that include antigen-presenting cells, T cells, B cells, and immunoglobulins.

Newborn infants are immunologically naïve. Although this is true for all newborn infants, premature infants are especially compromised due to immature defense mechanisms. Thus, the response to infection by newborn infants is largely dependent on innate, nonspecific, and quickly recruitable host defenses rather than on the adaptive, specific defenses that require time to develop pools of lymphocytes and antibodies that are specific to the inciting antigenic stimulus.

The innate host defenses, both cellular and secreted/soluble elements, recognize structurally conserved molecular sequences that are shared among groups of pathogens. These sequences are called "pathogen-associated molecular patterns" (PAMPS) and include lipopolysaccharides (gram-negative bacteria), lipoteichoic acids (gram-positive bacteria), bacterial lipoproteins or peptidoglycans, mycobacterial glycolipids, fungal mannans, bacterial DNA sequences, and double-stranded RNAs. PAMPS are recognized by "pattern recognition receptors" (PRRs) present on cellular elements (such as phagocytes and epithelial and endothelial "barrier" defense cells), and soluble or secreted elements (such as complement, fibronectin, defensins, cathelicidins, lysozyme, collectins, and nitric oxide). PRRs are germline encoded and do not depend on clonal expansion and development of immunologic memory.

The cellular elements of the innate host response within the lung include resident alveolar macrophages and dendritic cells and recruited polymorphonuclear (PMN) and mononuclear leukocytes. Macrophages in the lung, like elsewhere in the body, are primary effector cells of innate immunity. (Figure)

In response to microbial or particulate antigens, alveolar macrophages are important for phagocytosis, microbial killing, local immune modulation, and antigen presentation to initiate immunologic memory and adaptation. Alveolar macrophages recognize and are activated by a number of PAMPs such as lipopolysaccharide, surfactant proteins A and D, Fc portions of immunoglobulins, complement components (C1q and C3b), mannose, and fibronectin. As an example, the lipopolysaccharide associated with endotoxin binds to the sentinel cellular PRR for alveolar macrophage activation called CD14. The activated CD14 receptor then binds to a family of highly conserved receptors called toll-like receptors (TLRs) that provide specificity to the innate immune response. Individual TLRs recognize different microbial pathogens (TLR4-endotoxin, TLR2-gram-positive bacteria, mycobacteria and yeast, TLR3-viral messenger RNA, TLR9-bacterial DNA). Following ingestion, the microbe is killed by degradation by enzymes (such as lysozyme, proteases, hydrolases) and by reactive oxygen and nitrogen species (such
as superoxide anion, hydrogen peroxide, hydroxyl radical, singlet oxygen, and nitric oxide). Activation of the "early response" cellular signaling pathways generate cytokines, such as tumor necrosis factor and interleukin-1β, that amplify the inflammatory response and recruit lymphocytes and dendritic cells to commence an adaptive immune response. Neonatal alveolar macrophages demonstrate impaired phagocytosis and microbial killing (especially of bacteria and fungi) compared with adult macrophages. Furthermore, neonatal alveolar macrophages have an impaired response to proinflammatory mediators (such as interferon gamma) that impedes recruitment of other inflammatory cells, cytokine production, and the adaptive immune response.

Polymorphonuclear leukocytes are recruitable phagocytes that can be rapidly mobilized in response to infection and inflammation. The pulmonary circulation provides a major reservoir of marginated PMNs in newborn infants and adults. Neonatal PMNs, however, do not function as well as adult PMNs in a number of ways. PMN production during inflammation, half-life, responsiveness to endotoxin, endothelial binding (due to low L-selectin on PMN membranes and limited ability to upregulate B2-integrin expression), chemotaxis, and phagocytosis with low opsonic activity are deficient. Thus, the impaired immune response of neonatal PMNs increases the risk of infection in newborn infants compared with adults.

Dendritic cells are accessory immune cells primarily serving to present antigen to lymphocytes during the adaptive immune response. Phagocytic and microbicidal function is limited. Neonatal dendritic cells are also less efficient at presenting antigen to T-cells and do not produce interferon gamma as well as adult dendritic cells. These deficiencies delay expansion of memory T cells and increase the risk of infection. Other lung cells also contribute to immune activity.

Endothelial cells, like dendritic cells, express MHC class II molecules important for antigen presentation. Like phagocytic cells, they also produce and secrete cytokines and express TLRs important for adhesion, chemotaxis, recruitment, and activation of inflammatory cells at the "gate" between the vascular space and interstitium of the lung.

Pulmonary fibroblasts primarily function to produce structural and matrix proteins. As a secondary function, pulmonary fibroblasts respond to macrophage-derived tumor necrosis factor and interleukin-1 by production and secretion of inflammatory cytokines, thereby amplifying the local immune response.

Pulmonary epithelial cells function to maintain fluid balance within the lung, produce surfactant, provide a surface for gas exchange, and act as a physical barrier for movement of cells and inflammatory mediators. Epithelial cells express CD14 and TLR2 receptors that facilitate responsiveness to endotoxin stimulation. Epithelial-derived inflammatory mediators, cytotoxic nitric oxide, and production of chemoattractants for PMNs, mononuclear phagocytes, and T lymphocytes serve to augment the immune response. Airway epithelial cells also express intercellular adhesion molecule-1, which promotes phagocyte adherence and migration. Furthermore, airway epithelial cells can shed soluble receptors that bind free tumor necrosis factor, thereby modifying local cytokine-induced inflammation. Major histocompatibility complex receptors are also expressed on airway epithelial cells in response to cytokine stimulation. Thus, in addition to innate immune function, epithelial cells can present antigens to T lymphocytes to initiate adaptive host defense mechanisms.

References:


American Board of Pediatrics Content Specification(s):
Understand what cytokines regulate immune function
Know that cytokines regulate phagocyte development and function
Understand the cellular components of acute inflammation
Understand the vascular components of acute inflammation
A term infant with meconium aspiration syndrome and persistent pulmonary hypertension continues to be hypoxemic despite mechanical ventilation with 100% oxygen, surfactant treatment, and high-frequency oscillatory ventilation. An echocardiogram reveals an anatomically normal heart with suprasystemic right ventricular pressures and right to left shunting through the ductus arteriosus and foramen ovale consistent with a diagnosis of persistent pulmonary hypertension of the newborn (PPHN). Therapy with inhaled nitric oxide (iNO) is instituted with an immediate dramatic improvement in oxygenation. You are discussing with the pediatric resident the mechanisms for the improvement in oxygenation following iNO treatment and disease-specific responses to iNO.

Of the following, the condition MOST likely to respond dramatically to iNO is:

1. congenital diaphragmatic hernia
2. congenital pneumonia
3. idiopathic PPHN
4. meconium aspiration syndrome
5. respiratory distress syndrome

You selected 4, the correct answer is 3.

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Neonatal hypoxemic respiratory failure may be associated with widespread vasoconstriction of the pulmonary microvasculature, giving rise to intra- and extrapulmonary shunts and profound hypoxemia. This clinical syndrome has also been referred to as persistent pulmonary hypertension of the newborn (PPHN) because of the failure of the elevated pulmonary vascular resistance (PVR) to decrease after birth in affected infants. PPHN has been associated with various neonatal diseases, such as meconium aspiration, group B streptococcal sepsis, or respiratory distress syndrome. Inhaled nitric oxide (iNO) is a Food and Drug Administration-approved selective pulmonary vasodilator used in the treatment of PPHN. iNO causes pulmonary vasodilatation by stimulating soluble guanylate cyclase and increasing cyclic guanosine monophosphate content in vascular smooth muscle. The ability of iNO to selectively lower PVR and to decrease extrapulmonary venoarterial admixture accounts for the acute improvement in oxygenation observed in newborns with PPHN.

Pulmonary parenchymal disease, including meconium aspiration, respiratory distress syndrome, and pneumonia, accounts for approximately 80% of PPHN cases. In some neonates, PPHN is seen in the absence of pulmonary
parenchymal pathology (idiopathic PPHN). Metaanalysis of randomized trials has demonstrated that iNO improves oxygenation and reduces the need for extracorporeal membrane oxygenation in term infants with PPHN undergoing conventional mechanical ventilation.

Disease-specific responses to iNO have clearly been described. For example, patients with extrapulmonary right-to-left shunting show acute improvement in oxygenation when PVR becomes subsytemic during iNO treatment; however, patients with predominantly intrapulmonary shunting (pulmonary parenchymal disease) have less dramatic responses. Early studies have demonstrated that the effects of iNO may be suboptimal when lung volume is decreased in association with pulmonary parenchymal disease, for several reasons.

- Atelectasis and air space disease (pneumonia, pulmonary edema) may decrease the effective delivery of iNO to its site of action in terminal lung units.
- In cases complicated by severe lung disease and underinflation, pulmonary hypertension may be exacerbated because of the adverse mechanical effects of underinflation on PVR.
- Overinflation may lead to inadvertent gas trapping, vascular compression, and elevated PVR.

The above factors commonly complicate the treatment of infants with asymmetric lung disease or airway obstruction, as observed in meconium aspiration syndrome, pneumonia, or respiratory distress syndrome. In fact, patients not responding to iNO can show marked improvement in oxygenation with adequate lung inflation alone.

In newborns with severe lung disease, high-frequency oscillatory ventilation (HFOV) is frequently used to optimize lung inflation and minimize lung injury. In clinical pilot studies using iNO, the combination of HFOV plus iNO caused the greatest improvement in oxygenation in newborns with severe PPHN complicated by diffuse parenchymal lung disease and underinflation. A randomized, multicenter trial demonstrated that treatment with HFOV plus iNO was often successful in patients with severe PPHN who failed to respond to HFOV or iNO alone, and differences in responses were related to the specific disease. For patients with PPHN associated with severe lung disease, response rates were better with HFOV plus iNO than with HFOV alone or iNO and conventional ventilation. In contrast, for patients without significant parenchymal lung disease, both iNO and HFOV plus iNO were more effective than HFOV alone. This response to combined treatment with HFOV plus iNO likely reflects both improvement in intrapulmonary shunting and augmented iNO delivery to its site of action.

Neonates with congenital diaphragmatic hernia represent a unique group with hypoxemic respiratory failure. Although iNO may be effective in some patients, as a group, neonates with congenital diaphragmatic hernia are poor responders. This may be due to several factors including pulmonary hypoplasia, left ventricular size and function, as well as structural abnormalities of the pulmonary vascular bed.

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Images Pediatr Cardiol. 2002(10):4-29

Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev. 2001(4):CD000399


American Board of Pediatrics Content Specification(s):

- Identify the causes of and the effects of ventilation/perfusion mismatching
- Understand the pathogenesis, pathophysiology, and risk factors of persistent pulmonary hypertension
- Know the management of persistent pulmonary hypertension
- Understand the effects of administration of inhaled nitric oxide
An infant is delivered by elective, repeat cesarean section at an estimated gestational age of 36 weeks. The mother has had no labor. The infant at birth has tachypnea, chest retractions, and cyanosis that warrant administration of oxygen and continuous positive airway pressure. The chest radiograph shows bilateral haziness and fluid in the lung fissures.

Of the following, the MOST important factor in the rapid removal of fluid from the lung at the time of birth is:

1. active transcellular sodium absorption
2. hydrostatic gradient between lung interstitium and lumen
3. lymphatic clearance of lung fluid
4. osmotic gradient between lung interstitium and lumen
5. thoracic pressure during vaginal delivery

You selected 2, the correct answer is 1.

Do you want to add anything to your Learning Plan? (You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The infant in this vignette has evidence of retained lung fluid that has caused respiratory distress. Cesarean section delivery without preceding labor might have contributed to this lung fluid retention. The fetal lung is filled with fluid secreted by the developing lung epithelia. The rate and volume of fluid secreted into the fetal lung are calibrated to maintain lung volume at about functional residual capacity, and they are the major determinants of normal lung growth. Active chloride transport is the mechanism for lung fluid secretion (Figure 1).

Figure 1: Model of fetal lung fluid secretion by epithelial cell (adapted from Elias [2006])
At birth, effective transition from placental to pulmonary gas exchange requires removal of approximately 100 mL of fetal lung fluid. The process of emptying the lung begins before birth, is augmented by labor, and is mostly complete after two hours of independent breathing. Fluid is removed from the lung lumen by a combination of mechanical drainage and fluid absorption across the lung epithelium.

Decrease in lung fluid volume before labor likely involves mechanical forces, such as active fetal exhalation. The process of labor itself has been considered to be an important factor in the removal of lung fluid. It was previously believed that a significant amount of lung fluid is "squeezed" out of the lungs by thoracic compression during vaginal delivery. However, the fact that this decrease in lung fluid is seen not only in term animals delivered vaginally, but also in those delivered by cesarean section after the onset of labor suggests that labor itself induces other nonmechanical processes that are responsible for the lung fluid clearance. These mechanisms involve active transcellular sodium absorption by the high energy Na⁺/K⁺ ATPase pump on the basolateral membrane and epithelial Na⁺ channel (ENaC) on the apical epithelial membrane that drives fluid out of the lumen into the interstitial space (Figure 2).

Figure 2: Model of fetal lung fluid absorption by epithelial cell (adapted from Elias [2006])

Most interstitial fluid moves into the fetal/newborn pulmonary circulation, and some drains via the lymphatics. Starling forces that may assist fluid absorption
(that is, osmotic pressure and hydrostatic gradients between the lung interstitium and the lung lumen) do not change during labor and are not thought to play a role in the removal of fetal lung fluid. The active fluid absorption is further accelerated after birth, and most of the fluid is cleared from the term newborn lung within two hours of independent breathing.

The active absorption mechanism is switched on by the perinatal epinephrine surge associated with labor and delivery. This epinephrine responsiveness is absent in the immature fetal lung and is induced in the last half of gestation by the rise in active thyroid and steroid hormones in the fetal circulation. The increase in oxygen tension associated with the onset of air breathing at birth consolidates the switch to fluid absorption. Because the absorptive mechanism of the fetal lung develops in the latter part of gestation, infants who are born prematurely may have restricted ability to clear fluid from their lungs.

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References:


American Board of Pediatrics Content Specification(s):

Know the mechanism of production and clearance of fetal lung fluid, its contribution to amniotic fluid, and its importance to fetal lung development

Understand the pathogenesis, pathophysiology, and risk factors of transient tachypnea of the newborn infant
A full-term baby girl was born to a woman who had been diagnosed with interstitial pneumonitis as a child. The infant’s maternal grandfather had died of lifelong lung disease of unknown cause. The infant developed respiratory symptoms of tachypnea and cyanosis while breathing room air at 6 weeks of age. Physical examination was remarkable for tachypnea, cyanosis, and intercostal and subcostal retractions. Systemic blood pressure was within normal limits. Radiography of the chest showed hyperinflation with increased interstitial markings. An echocardiogram showed normal cardiac anatomy and function. Blood and urine cultures were sterile. Respiratory cultures showed normal flora and absence of respiratory viruses. The infant's respiratory status worsened over the next few days, necessitating assisted ventilation. A workup for cystic fibrosis and immune deficiency was negative. Based on the family history, open-lung biopsy was performed. Lung histopathology revealed nonspecific interstitial pneumonitis.

Of the following, the protein MOST likely to be abnormal in the infant in this vignette is:

1. lipid transport protein ABCA3
2. surfactant protein A
3. surfactant protein B
4. surfactant protein C
5. surfactant protein D

You selected 3, the correct answer is 1.

Do you want to add anything to your Learning Plan?
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Pulmonary surfactant is required for adaptation to air breathing after birth, reducing surface tension at the air-liquid interface in the alveolus to maintain lung volumes during the respiratory cycle. Deficiency of pulmonary surfactant is associated with respiratory distress syndrome (RDS) in preterm infants, a common cause of infant morbidity and mortality. Though much less frequently reported, surfactant deficiency can also lead to acute and chronic lung disease in term newborn infants and older children.

Pulmonary surfactant is a lipid/protein complex that is synthesized by type II epithelial cells lining the alveoli of the lungs. Phospholipids comprise approximately 90% of pulmonary surfactant, of which 70% to 80% is phosphatidylcholine (PC) and 10% is phosphatidyglycerol (PG), and the remainder includes minor amounts of phosphatidylinositol (PI),
phosphatidylethanolamine (PE), phosphatidylserine (PS), and sphingomyelin (SM) (Figure 1).

Figure 1: Composition of surfactant from the mature lung (from Jobe [2006]).

Pulmonary surfactant is unique in its high PC content; the dipalmitoyl form (DPPC), the major surface-active phospholipid component of pulmonary surfactant comprises approximately half of the PC. Proteins constitute 8% to 10% of surfactant and include the hydrophilic proteins (surfactant proteins [SP] A and D) and the small hydrophobic proteins (SP-B and SP-C). In contrast to the hydrophilic SP-A and SP-D, the hydrophobic SP-B and SP-C directly affect the biophysical properties of surfactant lipids both in vivo and in vitro, and are critically important for surfactant function. SP-B and SP-C work cooperatively to optimize rapid absorption and spreading of phospholipids on a surface and to facilitate the development of low surface tensions on surface area compression. Surfactants prepared by organic solvent extraction of natural surfactants or from lung tissue contain SP-B and SP-C, but lack SP-A.

Surfactant lipids are synthesized primarily in the endoplasmic reticulum of the alveolar type II cells and are transferred via the Golgi system to the lamellar bodies (Figure 2).

Figure 2: Basic pathways for surfactant metabolism (from Jobe [2006]).
Within the type II cell, the lamellar body is the storage compartment for pulmonary surfactant-associated lipids and for the hydrophobic SP-B and SP-C. Lamellar bodies are secreted into the air space in response to stretch, β-adrenergic, and purinergic agonists. Transport of lamellar bodies is regulated by the ABCA3 transporter molecule, which is found in the limiting membrane of these organelles. After exocytosis, lamellar bodies unravel and undergo a dramatic change in ultrastructural morphology, producing tubular myelin that represents the major extracellular pool of surfactant lipids from which mono- and multilayered films are formed. The lipid-rich films spread at the air-liquid interface in the alveoli and reduce surface tension, preventing alveolar collapse.

Surfactant is inactivated by mechanical and biological processes and converted into the surface-inactive, small aggregate which is taken up by alveolar type II cells, and reutilized or catabolized. Alveolar macrophages internalize and degrade small surfactant aggregate remnants under control of the signaling of granulocyte-macrophage colony-stimulating factor (GM-CSF). Indeed, deletion of the genes encoding GM-CSF or its receptor, or presence of autoantibodies that block GM-CSF activity cause an accumulation of surfactant that is characteristic of pulmonary alveolar proteinosis in mice and humans. Intracellular and extracellular surfactant pool sizes are precisely maintained by the regulation of synthesis, secretion, reuptake, reutilization, and catabolism.

The disease pattern presented in this vignette is most consistent with deficiency of SP-C. SP-C, like SP-B, is a small hydrophobic protein. The human SP-C gene has been localized to the short arm of chromosome 8. Processing of the SP-C pro-protein is linked to SP-B expression. Unlike SP-B gene mutations, which lead to respiratory distress soon after birth, SP-C deficiency usually presents a few months later as interstitial lung disease. The clinical presentation varies from mild tachypnea, respiratory distress, and failure to thrive to progressive respiratory failure. At present, there is no definitive treatment for respiratory failure associated with mutation of SFTPC; however, lung transplantation may be an option. Histopathologic features include alveolar inflammation, pulmonary infiltration with monocytes and macrophages, a progressive loss of alveolar structure, and pulmonary fibrosis. There is generally no history or detectable evidence of viral infection, and SP-C is undetectable in the lung tissue on biopsy. Disorders in SP-C are generally inherited as autosomal-dominant genes with variable penetrance. Diagnosis of congenital SP-C-related lung disease can be made by sequencing of the SFTPC gene. Mutation in SFTPC with resultant SP-C deficiency that presents as respiratory failure in the neonatal period is a rare
Surfactant protein A, like SP-D, belongs to a family of proteins named collectins because it has collagenous and lectin-binding domains. SP-A is the most abundant surfactant-associated protein and was the first to be described. SP-A has a central role in tubular myelin formation and metabolism and function of surfactant, as well as in host defense. Genetic studies show that certain SP-A polymorphisms are clearly associated with an increased severity of RDS and the subsequent development of chronic lung disease in premature infants. However, no mutations of the translated portions of the SP-A genes have been reported in humans. SP-A is not contained in surfactants used for treatment of RDS.

Human SP-B is a small, 79-amino-acid, amphipathic peptide encoded by a single gene located on chromosome 2 and produced in type II epithelial cells lining the alveoli. Extracellular SP-B plays a critical part in surfactant homeostasis by promoting adsorption of lipid molecules into the expanding surface film and enhancing their stability during the compression and expansion that occur during the respiratory cycle. It is an active component of surfactant-replacement preparations used in the treatment of RDS in preterm infants. The level of SP-B is low in preterm infants who are at risk for RDS. In contrast to SP-A, genetic disruption of SP-B expression causes an unambiguous neonatal respiratory phenotype in both human infants and mice.

Surfactant protein B deficiency was the first reported genetic cause of lethal RDS in infants and is present in 15% of term infants dying of a syndrome similar to RDS. Symptoms are generally observed before 12 hours of age. History of affected family members and/or consanguinity has been associated with the disorder. Radiographic findings include diffuse alveolar infiltrates, alveolar collapse, reticular-granular infiltrates, and air bronchograms in full-term infants without other underlying causes of respiratory failure. In spite of oxygen and assisted ventilation, surfactant replacement and/or extracorporeal membrane oxygenation (ECMO), most infants die in the first week or month after birth. Surfactant replacement is not effective; the infants generally have no or transient responses to therapy. Some infants have undergone lung transplantation with prolongation and improvement of life. Definitive diagnosis is made by identification of mutations in both alleles of the SFTPB gene. Marked histologic abnormalities are observed in the lung at autopsy or biopsy, with evidence of diffuse alveolar and bronchiolar damage, atelectasis, hyaline membranes, interstitial thickening, type II cell hyperplasia, and accumulation of alveolar macrophages and proteins in the alveoli. Uncommon mutations that cause a partial deficiency of SP-B have been associated with chronic interstitial lung disease in childhood.

Surfactant protein D is a member of the collectin family and is expressed in pulmonary and extrapulmonary tissues. Its functions include carbohydrate-domain recognition on the surface of pathogens. In vitro experiments suggest that SP-D, like SP-A, is involved in the first line of defense against inhaled pathogens. Unlike the case with SP-A, there are no reports of SP-D polymorphisms conferring a higher risk of RDS or neonatal bronchopulmonary dysplasia. Certain SP-D (and SP-A) polymorphisms have been linked to increased susceptibility to chronic obstructive pulmonary disease in a Mexican population and childhood infection with respiratory syncytial virus. No human infant or older individual with respiratory distress and mutation in the SP-D gene has been identified.

The ABCA3 protein is a member of the adenosine triphosphate (ATP)-binding cassette (ABC) protein family, which is a family of transmembrane proteins involved in membrane trafficking. The ABCA subgroup of proteins is predominantly involved in lipid transport across membranes. The gene for ABCA3 is expressed in type II cells, and the protein localizes to lamellar bodies, suggesting that it may have an important role in surfactant metabolism.

Mutations in other ABC proteins result in human diseases, including ABCA1
(Tangier disease, a disorder associated with cholesterol accumulation in macrophages and peripheral tissues and absence of high-density lipoproteins), \(ABCA4\) (forms of retinal degeneration), and \(ABCA12\) (congenital ichthyoses). Mutations in \(ABCA3\) in humans have been associated with autosomal recessive lung disease in newborn infants. The diagnosis of \(ABCA3\) deficiency should be suspected in full-term infants with respiratory failure unresponsive to conventional management and family history of consanguinity and neonatal losses due to respiratory failure. Radiographic findings associated with \(ABCA3\) mutations are consistent with RDS in newborn infants. Diffuse pulmonary opacification, reticular-granular infiltrates, and air bronchograms are observed. Infants present with grunting, retractions, and cyanosis in the first days of life, and rapidly develop respiratory failure that is refractory to ventilation, surfactant replacement, and ECMO. Histopathologic changes include alveolar proteinosis, infiltration by alveolar macrophages, alveolar wall thickening, and type II cell hyperplasia. Electron microscopy demonstrates small, abnormally dense lamellar body-like organelles, and the absence of normal lamellar bodies in type II epithelial cells. In contrast to patients with \(SFTPC\) mutations, in most patients with \(ABCA3\) mutations, the onset of lung disease is in the neonatal period. In some patients with \(ABCA3\) mutations, the onset of symptoms is later in childhood, so that there is a clinical overlap with interstitial lung disease caused by \(SFTPC\) mutations.

A report reviewing 300 term infants with a severe RDS syndrome found that about 14% had \(SP-B\) deficiency, and about 14% had deficiency of the ATP-binding cassette transporter gene, \(ABCA3\). If this clinical series is representative, then about 33% of severe lethal RDS in term infants is explained by mutations in genes essential for surfactant metabolism. Most of the other infants probably also have undescribed mutations as an explanation for their respiratory failure. In another report, DNA samples from 195 children with chronic lung disease of unknown origin were analyzed. In this population of children with chronic lung disease, 5% had the common \(ABCA3\) mutation (E292V) in contrast to 14% who had an \(SP-C\) mutation and 1% who had an \(SP-B\) mutation.

In summary, mutations in the genes encoding \(SP-B\), \(SP-C\), and \(ABCA3\) disrupt surfactant homeostasis within type II epithelial cells and cause respiratory distress in newborn infants. Together these genes represent a relatively rare cause of acute and chronic lung disease in newborn infants and children. Diagnosis of the inherited disorders of surfactant homeostasis should be suspected in full-term infants with acute or chronic respiratory disease that is refractory to conventional treatments. Both biochemical and genetic tests can be helpful in making a definitive diagnosis of familial disorders of surfactant homeostasis and in the treatment and genetic counseling of affected infants and their families.

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References:


American Board of Pediatrics Content Specification(s):

Understand the effects of surface tension on alveolar and airway stability and lung mechanics (LaPlace law)

Understand the pathophysiology of RDS

Understand the risk factors for RDS

Recognize the clinical features of RDS

Recognize the laboratory features of RDS

Recognize the radiographic features of RDS

Recognize the pathologic features of RDS

Understand the prevention of RDS

Understand the management of RDS, including surfactant replacement

Understand the risk factors for bronchopulmonary dysplasia/chronic lung disease
A term female infant is delivered by emergency cesarean section because of acute fetal distress. The fetal heart rate monitor indicated bradycardia (60 beats per minute) and absence of beat-to-beat variability. The pregnancy was otherwise uncomplicated. The infant had apnea, hypotonia, bradycardia, and cyanosis. Although her heart rate improves with positive pressure ventilation and fraction of inspired oxygen (FiO₂) of 1.0, she continues to have tachypnea and cyanosis. Capillary refill is 4 to 5 seconds. After mechanical ventilation and volume resuscitation is initiated, oxygen saturation (SpO₂) measured on the right hand reads 87% and capillary refill is 2 seconds. The postductal SpO₂ measured on the left foot reads 74%. The systolic blood pressure is 76 mm Hg. The chest radiograph shows a normal cardiothymic silhouette, lung expansion to the 9th rib, and dark lung fields. An echocardiogram reveals normal cardiac anatomy, elevated pulmonary artery pressures, flattened ventricular septum, and right to left shunting across the ductus arteriosus.

Of the following, the factor that MOST contributes to the physiologic aberrations in this infant is:

1. atelectasis
2. hypotension
3. hypoxemia
4. lung hypoplasia
5. shear stress

You selected 3, the correct answer is 3.

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During the fetal state, pulmonary vascular resistance is elevated and blood flow is diverted such that only approximately 8% of cardiac output traverses the lung. Hypoxic vasoconstriction, mechanical compression, and distortion of the pulmonary blood vessels caused by fluid-filled alveoli and low lung volume, low systemic vascular resistance (low resistance placental circulation), and active pulmonary vascular tone cause the pulmonary blood flow to be low. During the early fetal period, an underdeveloped pulmonary vascular tree and relatively high activity of vasoconstriction mediators (such as endothelin, thromboxanes, leukotriene D4) compared to vasodilator activity also contribute to pulmonary vasoconstriction.

Progressive growth and proliferation of the pulmonary vascular tree are expected to decrease pulmonary vascular resistance with increasing gestation. Concentrations of vasoconstricting mediators such as endothelin also begin to decline late in
gestation. However, hypoxic vasoconstriction continues to affect the newly developed pulmonary vasculature. The net effect is that hypoxic vasoconstriction predominates over the vasodilator effects of a larger vascular bed and lower concentrations of vasoconstricting agents. Thus, pulmonary vascular resistance remains elevated.

When the fetus is near term, nitric oxide concentrations in the pulmonary endothelium increase and cause vasodilatation through the nitric oxide/cyclic guanosine monophosphate pathway. Prostacyclin concentrations also increase and induce vasodilatation in the lung through cyclic adenosine monophosphate (AMP). Activation of potassium channels on endothelial cells by cyclic AMP leads to vascular smooth muscle relaxation by a direct effect of myosin phosphorylation and/or through activation of a cyclic AMP-dependent kinase. Furthermore, cyclooxygenase activity increases the production of vasodilating prostaglandins E1, E2, D2, and H2. The stimuli for these preparatory changes in the pulmonary endothelial function are unclear. However, these changes prepare the fetus for transition to a postnatal circulation at birth.

The transition from the fetal to postnatal circulation at birth is dramatic. Rhythmic lung distension, resolution of hypoxic vasoconstriction (elevation in oxygen tension), and shear stress-associated vasodilatation initiate production of a cascade of endogenous vasodilators (such as nitric oxide, prostacyclin, and bradykinin) and reduce the production of endogenous vasoconstrictors (such as endothelin-1, thromboxanes, norepinephrine, and angiotensin-1). The net effect is an increase in pulmonary blood flow, left atrial preload, left ventricular output, and gas exchange. During the following days and weeks, the pulmonary vascular bed becomes fully recruited, the endothelial and vascular smooth muscle cells spread, and arterial muscularization of the pulmonary arterioles decreases. Pulmonary vascular resistance thereby falls to adult levels.

Infants with persistent pulmonary hypertension fail to make the transition from a fetal circulatory pattern due to persistent elevation of the pulmonary vascular resistance. Pulmonary vascular muscularization is abnormally increased, and the effects of vasoconstricting mediators dominate over the insufficient or impaired activity of vasodilating mediators especially during ongoing hypoxia (Figure 1).

**Figure 1:** Hypoxia increases thromboxane A (TxA2): prostacyclin (PGI) ratio, G-protein coupled receptor activation, and endothelin-1 (ET-1 Gq/11R), all of which cause calcium mobilization and contraction of smooth muscle cells (vasoconstriction). Hypoxia decreases PGI and nitric oxide (NO) concentrations which facilitate vasoconstriction and increases calcium sensitivity. Hypoxia also reduces potassium channel activity which facilitates contraction. Hypoxia increases concentrations of hypoxia-inducible factor 1 alpha (HIF-1alpha) and vascular endothelial growth factor (VEGF) which induce proliferation of smooth muscle. Calcium mobilization and smooth muscle contraction also induce smooth muscle proliferation. COX-2, cyclooxygenase; eNO, endothelial nitric oxide; HIF-1alpha, hypoxia inducible factor 1 alpha; Ca, calcium; VEGF, vascular endothelial growth factor; sGC, soluble guanylate cyclase; cGMP, cyclic guanosine monophosphate; IP3, inositol triphosphate. (Adapted from Dakshinamurti [2005].)
It is also notable that nitric oxide and other vasodilators modulate the proliferation of vascular smooth muscle cells in addition to their vasodilator effects. Furthermore, smooth muscle proliferation is stimulated by endothelin-1, other vasoconstrictors, and hypoxia through hypoxia-inducible factor and vascular endothelial growth factor. It is likely that abnormal smooth muscle proliferation in the fetus is associated with abnormally low or high activity of vasoactive and mitogenic mediators.

Shear stress-associated vasodilatation in the normal fetus occurs through an increase in smooth muscle membrane potassium permeability caused by turbulent, high-pressure blood flow (Figure 2).

Figure 2: Shear stress due to turbulent, high flow induces endothelial nitric oxide (eNO) synthase, production of cyclic guanosine monophosphate (cGMP) and vasodilation. Wall strain overstretches smooth muscle cells, induces calcium sensitization that increases vasoreactivity to agonists, and increases the myogenic contractile response. Smooth muscle cell proliferation and hypertrophy also result from increased myogenic activity. Inositol triphosphate (IP₃) is also induced by wall strain and results in vasoconstriction. NO, nitric oxide; Ca, calcium; sGC, soluble guanylate cyclase. (Adapted from Dakshinamurti [2005].)
If the walls of pulmonary blood vessels are strained by being overstretched, however, nitric oxide synthase activity and endothelium-dependent vasodilatation is impaired and myogenic vasoconstriction occurs. Myogenic vasoconstriction is exacerbated by enhanced proliferation and calcium sensitization of smooth muscle cells in response to pulmonary vascular wall strain. Myogenic contraction is especially evident in pathologic states such as persistent pulmonary hypertension of the newborn.

When pulmonary vascular resistance is elevated in the hours and days after birth, venous blood may be diverted across the ductus arteriosus, foramen ovale, or poorly functioning lung, mix with the arterial circulation, and cause hypoxemia. Hypoxic vasoconstriction further complicates the primary medical disorders associated with persistent pulmonary hypertension, such as meconium aspiration syndrome, septic shock, congenital diaphragmatic hernia, transient tachypnea, and respiratory distress syndrome. The infant in this vignette has primary persistent pulmonary hypertension that is characterized by abnormal distal pulmonary vascular muscularization and increased vasoreactivity during hypoxia.

The vignette describes an infant who has severe hypoxemia. Of the answer choices, hypoxemia is the factor that most contributes to pulmonary vasoconstriction and elevated pulmonary vascular resistance. The infant is receiving FiO₂ of 1.0 and positive pressure ventilation with adequate lung expansion (ie, no atelectasis or pulmonary hypoplasia), and has a normal blood pressure. Shear stress within the pulmonary vasculature is expected to increase pulmonary vasodilatation; pulmonary vascular strain induced by high flow, high intravascular pressure, and excessive endothelial and smooth muscle cell stretch cause vasoconstriction.

References:


Ghanayem NS, Gordon JB. Modulation of pulmonary vasomotor tone in the fetus and neonate. Respir Res. 2002;2:139-144


American Board of Pediatrics Content Specification(s):

Understand the factors affecting and regulating the pulmonary circulation in the fetus and newborn infant and during the transitional period

Understand the pathogenesis, pathophysiology, and risk factors for persistent pulmonary hypertension
March: Question 4

A female neonate was delivered by vaginal route by a 26-year-old gravida 2, para 1 healthy white woman at 40 weeks’ gestation. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Approximately 2 hours after delivery, the infant developed progressive respiratory distress requiring assisted ventilation. Initial arterial blood gas measurements on conventional ventilation with 100% oxygen were pH 7.30, PCO2 57 mm Hg, and PO2 28 mm Hg. Chest radiography showed bilateral hazy opacities of both lungs with air bronchograms. There was a transient improvement in oxygenation following surfactant treatment. Echocardiography showed a structurally normal heart and pulmonary hypertension. The infant continued to have profound hypoxemia in spite of treatment with high-frequency oscillatory ventilation (HFOV), and inhaled nitric oxide (iNO). She was supported with venoarterial extracorporeal membrane oxygenation (ECMO). She remained hemodynamically stable and underwent decannulation 165 hours after initiation of ECMO. Her cardiopulmonary status progressively deteriorated over the subsequent 48 hours despite intravenous vasopressors, HFOV, and iNO, and she died on the 10th day after birth. Autopsy revealed alveolar type II cell hyperplasia, interstitial fibrosis, and diffuse alveolar damage.

Of the following, the protein MOST likely to be abnormal in the infant in this vignette is:

1. lipid transport protein ABCA12
2. surfactant protein A
3. surfactant protein B
4. surfactant protein C
5. surfactant protein D

You selected 1, the correct answer is 3.

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Pulmonary surfactant is required for adaptation to air breathing after birth, reducing surface tension at the air-liquid interface in the alveolus to maintain lung volumes during the respiratory cycle. Deficiency of pulmonary surfactant is associated with respiratory distress syndrome (RDS) in preterm infants, a common cause of infant morbidity and mortality. Although much less frequently reported, surfactant deficiency can also lead to acute and chronic lung disease in term newborn infants and older children.
Pulmonary surfactant is a lipid/protein complex that is synthesized by type II epithelial cells lining the alveoli of the lungs. Phospholipids comprise approximately 90% of pulmonary surfactant, of which 70% to 80% is phosphatidylcholine (PC), 10% is phosphatidylglycerol (PG), and the remainder includes minor amounts of phosphatidylinositol (PI), phosphatidylethanolamine (PE), phosphatidylserine (PS), and sphingomyelin (SM) (Figure 1).

Figure 1: Composition of surfactant from the mature lung (from Jobe 2006).

Pulmonary surfactant is unique in its high PC content; the dipalmitoyl form (DPPC), the major surface-active phospholipid component of pulmonary surfactant comprises approximately half of the PC. Proteins constitute 8% to 10% of surfactant and include the hydrophilic proteins (surfactant proteins [SP] A and D) and the small hydrophobic proteins (SP-B and SP-C). In contrast to the hydrophilic SP-A and SP-D, the hydrophobic SP-B and SP-C directly affect the biophysical properties of surfactant lipids both in vivo and in vitro, and are critically important for surfactant function. SP-B and SP-C work cooperatively to optimize rapid absorption and spreading of phospholipids on a surface and to facilitate the development of low surface tensions on surface area compression. Surfactants prepared by organic solvent extraction of natural surfactants or from lung tissue contain SP-B and SP-C, but lack SP-A.

Human SP-B is a relatively small, 79-amino-acid, amphipathic peptide encoded by a single gene located on chromosome 2 and produced in type II epithelial cells lining the alveoli. Extracellular surfactant protein B plays a critical part in surfactant homeostasis by promoting adsorption of lipid molecules into the expanding surface film and enhancing their stability during the compression and expansion that occur during the respiratory cycle. It is an active component of surfactant-replacement preparations used in the treatment of RDS in preterm infants. The level of SP-B is low in preterm infants who are at risk for RDS, as it is in adults who are at similar risk. In contrast to SP-A, genetic disruption of SP-B expression causes an unambiguous neonatal respiratory phenotype in both human infants and mice. SP-B deficiency was the first reported genetic cause of lethal respiratory distress syndrome in infants and is present in 15% of term infants dying of a syndrome similar to RDS. Symptoms are generally observed before 12 hours of age. History of affected family members and/or consanguinity has been associated with the disorder. Radiographic findings include diffuse alveolar infiltrates, alveolar collapse, reticular-granular infiltrates, and air bronchograms in full-term infants without other underlying causes of respiratory failure. In spite of oxygen and assisted ventilation, surfactant replacement and/or extracorporeal membrane oxygenation (ECMO), most infants die in the first week or month after
Surfactant replacement is not effective; the infants generally have no or transient responses to treatment. Some infants have undergone lung transplantation with prolongation and improvement of life. Definitive diagnosis is made by identification of mutations in both alleles of the SFTPB gene. Marked histologic abnormalities are observed in the lung at autopsy or biopsy, with evidence of diffuse alveolar and bronchiolar damage, atelectasis, hyaline membranes, interstitial thickening, type II cell hyperplasia, and accumulation of alveolar macrophages and proteins in the alveoli. Uncommon mutations that cause a partial deficiency of SP-B have been associated with chronic interstitial lung disease in childhood.

Surfactant lipids are synthesized primarily in the endoplasmic reticulum of the alveolar type-II cells and are transferred via the Golgi system to the lamellar bodies (Figure 2).

Figure 2: Basic pathways for surfactant metabolism (from Jobe 2006).

Within the type-II cell, the lamellar body is the storage compartment for pulmonary surfactant–associated lipids and for the hydrophobic SP-B and SP-C. Lamellar bodies are secreted into the airspace in response to stretch and β-adrenergic and purinergic agonists. Transport of lamellar bodies is regulated by the ABCA3 transporter molecule, which is found in the limiting membrane of these organelles. After exocytosis, lamellar bodies unravel and undergo a dramatic change in ultrastructural morphology, producing tubular myelin that represents the major extracellular pool of surfactant lipids from which mono- and multilayered films are formed. The lipid-rich films spread at the air-liquid interface in the alveoli and reduce surface tension, preventing alveolar collapse. Surfactant is inactivated by mechanical and biological processes and converted into the surface-inactive, small aggregate which is taken up by alveolar type II cells, and reutilized or catabolized. Alveolar macrophages internalize and degrade small surfactant aggregate remnants under control of the signaling of granulocyte-macrophage colony-stimulating factor (GM-CSF). Indeed, deletion of the gene encoding GM-CSF, the gene encoding the GM-CSF receptor, or autoantibodies that block GM-CSF activity causes an accumulation of surfactant that is characteristic of pulmonary alveolar proteinosis in mice and humans. Intracellular and extracellular surfactant pool sizes are precisely maintained by the regulation of synthesis, secretion, reuptake, reutilization, and catabolism.

Surfactant protein A, like SP-D, belongs to a family of proteins named collectins, because it has collagenous and lectin-binding domains. SP-A is the most abundant...
Surfactant-associated protein and was the first to be described. SP-A has central roles in tubular myelin formation, metabolism, and function of surfactant, as well as in host defense. Although genetic studies show that certain SP-A polymorphisms are clearly associated with an increased severity of RDS and the subsequent development of chronic lung disease (CLD) in premature infants, no mutations of the translated portions of the SP-A genes have been reported in humans. SP-A is not contained in surfactants used for treatment of RDS.

Surfactant protein C, like SP-B, is a small hydrophobic protein. The human SP-C gene has been localized to the short arm of chromosome 8. Processing of the SP-C pro-protein is linked to SP-B expression. Unlike SP-B gene mutations, which lead to respiratory distress soon after birth, SP-C deficiency usually presents at a few months of age as interstitial lung disease. The clinical presentation varies from mild tachypnea, respiratory distress, and failure to thrive to progressive respiratory failure. At present, although there is no definitive treatment for respiratory failure associated with mutation of SFTPC, lung transplantation may be an option. Histopathologic features include alveolar inflammation, pulmonary infiltration with monocytes and macrophages, a progressive loss of alveolar structure, and pulmonary fibrosis. There is generally no history or detectable evidence of viral infection, and SP-C is undetectable in the lung tissue on biopsy. Disorders in SP-C metabolism are generally inherited as autosomal-dominant genes with variable penetrance. Diagnosis of congenital SP-C–related lung disease can be made by sequence of the SFTPC gene. Mutation in SFTPC with resultant SP-C deficiency that presents as respiratory failure in the neonatal period is a rare entity.

Surfactant protein D is a member of the collectin family and is expressed in pulmonary and extrapulmonary tissues. Its functions include carbohydrate-domain recognition on the surface of pathogens. Unlike the case with SP-A, there are no reports of SP-D polymorphisms conferring a higher risk of RDS or of neonatal bronchopulmonary dysplasia. No human infant or older individual with respiratory distress and mutation in the SP-D gene has been identified. In vitro experiments suggest that SP-D, like SP-A, is involved in the first line of defense against inhaled pathogens. Only a small number of SP-D polymorphisms have been characterized. Certain SP-D (and SP-A) alleles have been linked to possible susceptibilities to chronic obstructive pulmonary disease in a Mexican population, and both SP-A and SP-D polymorphisms are associated with increased severity of childhood infection with respiratory syncytial virus.

The ABCA3 protein is a member of the adenosine triphosphate (ATP)–binding cassette (ABC) protein family, which is a family of transmembrane proteins involved in membrane trafficking. The ABCA subgroup of proteins is predominantly involved in lipid transport across membranes. The gene for ABCA3 is expressed in type II cells, and the protein localizes to lamellar bodies, suggesting that it may have an important role in surfactant metabolism. Mutations in other ABC proteins result in human diseases, including ABCA1 (Tangier disease, a disorder associated with cholesterol accumulation in macrophages and peripheral tissues and absence of high-density lipoproteins), ABCA4 (forms of retinal degeneration), and ABCA12 (congenital ichthyoses). Mutations in ABCA3 in humans have been associated with autosomal recessive lung disease in newborn infants.

The diagnosis of ABCA3 deficiency should be suspected in full-term infants with respiratory failure, failing conventional management, and with family histories of neonatal losses from respiratory distress, and consanguinity. Radiographic findings associated with ABCA3 mutations are consistent with RDS in the newborn infants. Diffuse pulmonary opacification, reticular-granular infiltrates and air bronchograms are observed. Infants present with grunting, retractions, and cyanosis in the first days after birth, and rapidly develop respiratory failure that is refractory to ventilation, surfactant replacement, and ECMO. Histopathologic changes include alveolar proteinosis, infiltration by alveolar macrophages, alveolar wall thickening, and type II cell hyperplasia. Electron microscopy demonstrates
small, abnormally dense lamellar body–like organelles and the absence of normal lamellar bodies in type II epithelial cells. In contrast to patients with \textit{SFTPC} mutations, in most patients with \textit{ABCA3} mutations, the onset of lung disease was in the neonatal period. In some patients with \textit{ABCA3} mutations, the onset of symptoms was later in childhood, so that there is a clinical overlap with interstitial lung disease caused by \textit{SFTPC} mutations.

In summary, mutations in the genes encoding \textit{SP-B}, \textit{SP-C}, and \textit{ABCA3} disrupt surfactant homeostasis within type II epithelial cells and cause respiratory distress in newborn infants. Together, these genes represent a relatively rare cause of acute and chronic lung disease in newborn infants and children. Diagnosis of the inherited disorders of surfactant homeostasis should be suspected in full-term infants with acute or chronic respiratory disease that is refractory to conventional treatments. Both biochemical and genetic tests can be helpful in making a definitive diagnosis of familial disorders of surfactant homeostasis and in the treatment and genetic counseling of affected infants and their families. A report reviewing 300 term infants with a severe RDS found that about 14% had \textit{SP-B} deficiency, and about 14% had deficiency of the ATP-binding cassette transporter gene, \textit{ABCA3}. If this clinical series is representative, then about 33% of severe lethal RDS in term infants is explained by mutations in genes essential for surfactant metabolism. Most of the other infants probably also have undescribed mutations as an explanation for their respiratory failure. In another report, DNA samples from 195 children with chronic lung disease of unknown etiology were analyzed. In this population of children with chronic lung disease, 5% had the common \textit{ABCA3} mutation (E292V) in contrast to 14% who had an \textit{SP-C} mutation and 1% who had an \textit{SP-B} mutation.

\textbf{References:}


**American Board of Pediatrics Content Specification(s):**

Understand the effects of surface tension on alveolar and airway stability and lung mechanics (LaPlace law)

Understand the pathophysiology of RDS

Understand the risk factors for RDS

Recognize the clinical features of RDS

Recognize the laboratory features of RDS

Recognize the radiographic features of RDS

Recognize the pathologic features of RDS

Understand the prevention of RDS

Understand the management of RDS, including surfactant replacement

Understand the risk factors for bronchopulmonary dysplasia/chronic lung disease
May: Question 6

A 2,200-g male infant is born to a 28-year-old primiparous woman at 34 weeks of estimated gestational age. The pregnancy was complicated by bilateral fetal pleural effusions, first detected on ultrasonography at 30 weeks' gestation. Worsening of the effusions during the ensuing weeks led to delivery by cesarean section. The infant's initial care includes thoracentesis which yields approximately 80 mL of amber fluid from each side of the chest. The pleural fluid reveals the following:

- Nucleated cell count, 560 cells/μL (560 × 10⁶ cells/L), with a differential count of
  - 93% lymphocytes
  - 5% neutrophils
  - 2% monocytes
- Glucose, 62 mg/dL (3.4 mmol/L)
- Protein, 2.8 g/dL (28 g/L)
- Triglyceride, 3.0 mg/dL (0.03 mmol/L)
- Cholesterol, 50 mg/dL (1.3 mmol/L)
- Lactate dehydrogenase, 90 U/L (1.5 μkat/L)

The infant's subsequent care includes drainage of pleural fluid through thoracostomy tubes, mechanical ventilation, enteral nutrition with milk rich in medium-chain triglycerides, and supplemental parenteral nutrition. At 14 days of age, the pleural fluid continues to reaccumulate in volumes approximating 50 mL from each side of the chest amounting to a cumulative fluid loss of approximately 1,400 mL. Other treatment options are considered.

Of the following, a PROMISING adjunctive treatment of pleural effusion in this infant is:

1. chemical pleurodesis
2. pleural abrasion
3. pleuroperitoneal shunt
4. somatostatin treatment
5. thoracic duct ligation

You selected 4, the correct answer is 1.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The infant in this vignette has clinical and laboratory evidence of congenital chylothorax. Congenital chylothorax, accumulation of chyle-containing lymphatic fluid in the pleural space, is the most common cause of pleural effusion that manifests during fetal and early neonatal periods. Its incidence is estimated at 1
in 6,000 to 1 in 10,000 live births; it is twice as common in males as in females. The analysis of pleural fluid is helpful in the diagnosis of congenital chylothorax. The fluid, in the absence of enteral feeding, typically is amber colored, is rich in lymphocytes (differential count >70%), and may not show a raised triglyceride concentration. With enteral feeding, especially using milk rich in long-chain triglycerides, the pleural fluid becomes milky in appearance, remains rich in lymphocytes, and shows a raised triglyceride concentration (>110 mg/dL [1.2 mmol/L]).

Congenital chylothorax may be transient and resolves spontaneously when it results from a potentially reversible obstruction or hypoplasia of the thoracic duct. Conversely, congenital chylothorax may be persistent and does not resolve spontaneously when it results from an intrinsic abnormality of the lymphatic system in the form of lymphangiomatosis or lymphangiectasia. The former represents sequestered lymphatic tissue in solitary or multifocal lesions; the latter represents distension of pulmonary subpleural and interlobular lymphatics. Persistent congenital chylothorax often is associated with other congenital malformations such as tracheoesophageal fistula and congenital heart defects; Noonan syndrome, Turner syndrome, and Down syndrome; and pulmonary abnormalities such as sequestration and congenital cystic adenomatoid malformation. The infant in this vignette has a clinical course suggestive of persistent congenital chylothorax.

Conventional management of persistent congenital chylothorax includes serial drainage of chyle, ventilatory assistance as needed, enteral nutrition with milk rich in medium-chain triglycerides, and supplemental parenteral nutrition. The loss of proteins and lymphocytes through drainage of chyle can result in hypoproteinemina, hypogammaglobulinemia, and lymphopenia, which may increase the risks of developing anasarca and nosocomial infection. Appropriate monitoring for infection and antimicrobial treatment, therefore, constitute an important aspect of management in such infants. Moreover, the loss of nutrients and electrolytes through drainage of chyle warrants close attention to nutritional status and fluid-electrolyte balance. In addition, the discomfort associated with thoracostomy tubes warrants judicious management of sedation and analgesia. When congenital chylothorax proves refractory to conventional management, additional treatment options require consideration.

Much of the evidence for the treatment of persistent congenital chylothorax stems from observational descriptive case studies. The rare occurrence of this disorder has precluded validation of the relative benefits of various treatment options through adequately powered randomized trials or systematic reviews. With this caveat, a comparison of different aspects of treatment such as invasiveness, safety, and efficacy based on observational studies suggests that somatostatin treatment is the most promising adjunctive treatment of persistent congenital chylothorax in the infant in this vignette.

Somatostatin, a 14-amino-acid peptide, is produced in multiple sites, including pancreatic d cells, the gastrointestinal tract, and the hypothalamus. Somatostatin causes selective vasoconstriction of arteriolar sphincters in the splanchnic circulation; it may induce a similar constriction of the intestinal lymphatics. The perturbation in the splanchnic circulation reduces chylomicron synthesis and its transport into the lymphatics. Somatostatin also inhibits gastrointestinal motility and release of various gastrointestinal hormones. It decreases gastric, pancreatic, and intestinal secretions as well as intestinal absorption and hepatic venous flow. Together, these actions account for reduced flow of chyle, which forms the rationale for the use of somatostatin as adjunctive treatment for congenital chylothorax.
The dose of somatostatin reported in case studies ranges from 3.5 μg/kg per hour (starting dose) to 10.0 μg/kg per hour (maximal dose). The preferred mode of administration is by continuous intravenous infusion. The duration of treatment varies between 7 and 14 days depending on the resolution of chylothorax or the emergence of side effects. The side effects are related primarily to the suppressive actions of somatostatin on gastrointestinal motility and secretions and include loose stools, flatulence, and emesis. Transient hypoglycemia, hypothyroidism, and liver dysfunction also have been described. Octreotide, a synthetic long-acting peptide analogue of somatostatin, may be used at a dose ranging from 1.0 μg/kg per hour to 7.0 μg/kg per hour by continuous intravenous or subcutaneous infusion in place of somatostatin.

Chemical pleurodesis involves intrapleural instillation of a sclerosing agent such as povidone-iodine. Iodine has strong oxidative and cytotoxic properties, which induce a potent inflammatory response in the pleural wall. The resultant sclerosis decreases the leakage of chyle into the pleural space, which is the rationale for the use of chemical pleurodesis in the treatment of persistent congenital chylothorax. In addition to being invasive, chemical pleurodesis is associated with numerous side effects of allergic sensitization including anaphylaxis, iodine-related impairment of thyroid function, renal dysfunction, and local cytotoxic mucosal and skin lesions.

Surgical abrasion of the pleura, placement of pleuroperitoneal shunt, and ligation of thoracic duct are invasive procedures of unconfirmed value in the treatment of persistent congenital chylothorax in neonates.

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References:


American Board of Pediatrics Content Specification(s):
Plan the therapeutic management of hydrothorax/chylothorax
You are called to an emergency delivery of a 41-week-gestation male infant born to a 37-year-old primiparous woman. Pregnancy was uncomplicated; findings on prenatal laboratory tests and ultrasonography were normal. The infant is lifeless on delivery; the heart rate is inaudible and he has no respiratory effort. Your team provides a full resuscitation according to the Neonatal Resuscitation Program guidelines; 6 minutes into the resuscitation the infant gasps.

Of the following, the change in intrathoracic pressure induced by gasping in this infant is MOST likely to decrease:

1. arterial carbon dioxide tension
2. cardiac output
3. cerebral blood flow
4. coronary perfusion pressure
5. venous return to the heart

You selected 1, the correct answer is 1.

Do you want to add anything to your Learning Plan?
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Gasping, also known as agonal respiration, is the terminal pattern of breathing that occurs after anoxia or ischemia and is a universal phenomenon in mammals. Gasping is especially prominent in the human newborn. Gasping is resuscitative to the extent that it produces gas exchange. Gasping respirations can be identified as having an extremely rapid rise of inspiratory activity. In a newborn infant, this pattern is seen before secondary apnea. According to the Neonatal Resuscitation Program (NRP), gasping respiration should be treated with positive pressure ventilation. Studies suggest that the frequency of gasping is predictive of the success of resuscitation.

A sharp increase in arterial oxygen saturation and a decrease in arterial carbon dioxide tension typically follow the gasp. This is associated with increased cardiac output, pulmonary blood flow and carbon dioxide elimination.

Changes in intrathoracic pressure induced by gasping increase the following:

- venous return to the heart
- aortic pressure
- coronary perfusion
- cardiac output and cardiac contractility

Improved cardiac output results in increased cerebral blood flow.
During the inspiratory phase of gasping the intrathoracic pressure decreases; this decrease in intrathoracic pressure is associated with a decrease in right atrial pressure. Thus, gasping generates a pressure gradient between the right side of the heart and vessels, which promotes venous return. During the expiratory phase of gasping, the intrathoracic and aortic pressures increase. The resulting increase in the pressure gradient between the aorta and right atrium favors coronary perfusion.

References:


American Board of Pediatrics Content Specification(s):

Understand the causes and pathophysiology, including cellular abnormalities, of acute asphyxia syndromes

Recognize the systemic complications and vascular redistribution of blood flow caused by hypoxia or asphyxia

Understand the proper approach to airway management in the delivery room

Know the indications for assisted ventilation in the delivery room
A term infant receives 2 days of antibiotics for suspected sepsis, and then is discharged from the hospital. One week later, you receive notification from your state metabolic laboratory of an elevated immunoreactive trypsinogen (IRT) concentration in the child. When you telephone the parents to explain the test results and ask for repeated testing, the infant's father asks, “My baby looks well, should I be worried?”

Of the following, the finding MOST predictive of a diagnosis of cystic fibrosis is:

1. elevated IRT concentration
2. heterozygosity for delta-F508
3. meconium ileus
4. mother with cystic fibrosis
5. rectal prolapse

You selected 3, the correct answer is 3.

Do you want to add anything to your Learning Plan? (You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Several findings in neonates suggest a diagnosis of cystic fibrosis. Meconium ileus has the highest positive predictive value for establishing a diagnosis of cystic fibrosis (80%-90%). The positive predictive values of several other findings in neonates for cystic fibrosis are as follows:

- elevated IRT on newborn screening–17%-25%
- rectal prolapse–11%
- mother with cystic fibrosis–8%
- heterozygosity for delta-F508–0.5%

The definitive diagnosis of cystic fibrosis is determined using clinical and laboratory criteria (Table 1).

Table 1. Diagnostic Criteria for Cystic Fibrosis (modified from Wallis 2006)
The gold standard for infants is the sweat chloride test, in which sweat is produced by pilocarpine iontophoresis and analyzed for chloride concentration. A concentration of more than 40 mEq/L is diagnostic in infants and more than 60 mEq/L is diagnostic in adults. Although it is difficult to obtain enough sweat (75 mg) from a newborn, many infants can be successfully tested after 3 weeks of age.

False-positive sweat chloride test results can be seen with hypothyroidism, Addison disease, ectodermal dysplasia, and glycogen storage disease, as well as laboratory errors due to evaporation or contamination. False negatives may be caused by edema or malnutrition.

The diagnosis of cystic fibrosis can be suggested by screening tests within the first week after birth. As of January 2007, 28 states required newborn screening for cystic fibrosis. Serum samples are checked for elevated levels of immunoreactive trypsinogen (IRT), a pancreatic enzyme released into the blood during pancreatic injury and during normal birth. It is recommended that an elevated IRT concentration on initial screening be followed up with another IRT test or DNA testing for the most common mutations.

The detection cutoff concentration for serum IRT is selected by each screening laboratory to provide the optimal sensitivity and specificity to detect cystic fibrosis. State screening programs looking for metabolic diseases other than cystic fibrosis generally pick screening criteria to give 20 to 50 false positives for each true positive, so that the test threshold is sensitive enough to detect most of the affected patients. For cystic fibrosis, in contrast, the chosen odds are 3 to 5 false positives for every true positive. Thus, a patient with an elevated IRT concentration has a 17% to 25% chance of having cystic fibrosis. False-positive results have been associated with conditions such as prematurity, asphyxia, cytomegalovirus infection, aneuploidies, and biliary atresia.

Universal state screening allows earlier diagnosis of cystic fibrosis than testing after the onset of symptoms. This early diagnosis results in improved growth, cognitive function, and survival compared with patients diagnosed after symptoms develop.

Cystic fibrosis is an autosomal recessive genetic disease involving the gene for the cystic fibrosis transmembrane regulator protein (CFTR) on chromosome 7. Each of the two alleles of the gene is abnormal in affected individuals, as is the case with most genetic biochemical defects. The most common gene defect in patients with cystic fibrosis is delta-F508, in which there is a deletion of the three DNA base-pairs coding for the 508th amino-acid residue of the CFTR protein. This residue is normally phenylalanine, abbreviated by biochemists as F, hence the F in delta-F508. The missing phenylalanine disables the function of CFTR, causing cystic fibrosis.

Of all the abnormal alleles for the CFTR gene in the US population, 70% have the mutation delta-F508. Heterozygosity for delta-F508 is found in 20% of patients with cystic fibrosis in the United States, with homozygosity in 50% of patients. Patients with cystic fibrosis who are
heterozygous for delta-F508 on one CFTR allele have an additional different defect in the other CFTR allele. In the general population, however, heterozygotes for delta-F508, with a normal CFTR gene on the other allele, have a risk of cystic fibrosis of 1 in 25 to 1 in 35. The incidence of the carrier state for a non–delta-F508 CFTR mutation is about 1% (between 1 in 80 to 1 in 120). To have cystic fibrosis, a heterozygote for delta-F508 would need to have inherited one of these non–delta-F508 mutations from a carrier, which would happen with a probability of half the carrier incidence, or about 0.5% of the time.

Adult female patients with cystic fibrosis have decreased fertility. Conception is made more difficult because of poor nutrition, which causes anovulation, and thickened cervical mucous, which acts as a barrier to sperm. Preterm delivery is common. Maternal mortality is increased, both during and soon after pregnancy, from nutritional and pulmonary complications. The child has a higher risk than the general population of having cystic fibrosis, because the mother will pass on one of her abnormal alleles for CFTR to the child. The risk to the child then becomes one half the risk of the father being a carrier of a CFTR gene abnormality. Assuming the father is a white North American and that no carrier testing has been done, the chance of the child having cystic fibrosis is about 8%.

The risk of the father being a carrier varies with his ethnic origin (Table 2).

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence, Population per case</th>
<th>Calculated Carrier Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>3,700</td>
<td>3%</td>
</tr>
<tr>
<td>North American Whites</td>
<td>2,500</td>
<td>4%</td>
</tr>
<tr>
<td>North American Hispanics</td>
<td>8,000</td>
<td>2%</td>
</tr>
<tr>
<td>African-Americans</td>
<td>17,000</td>
<td>1.5%</td>
</tr>
<tr>
<td>Asian-Americans</td>
<td>32,000</td>
<td>1%</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>1,700</td>
<td>5%</td>
</tr>
<tr>
<td>American Amish</td>
<td>640</td>
<td>8%</td>
</tr>
<tr>
<td>Brittany</td>
<td>377</td>
<td>10%</td>
</tr>
</tbody>
</table>

The carrier rate can then be estimated as twice the square-root of the incidence, using the Hardy-Weinberg equilibrium formula (http://en.wikipedia.org/wiki/Hardy-Weinberg_equilibrium).

Overall, the delta-F508 mutation accounts for 70% of all the abnormal CFTR alleles in the world, but more than 1,000 other CFTR gene defects have been identified. How could so many defects evolve, to cause such a severe disease in homozygotes? The answer appears to be in the protection given to heterozygotes. There is some evidence that heterozygotes for CFTR mutations have an advantage over people with two normal CFTR genes in surviving cholera, typhoid, and bronchial asthma.

In 10% to 20% of cases, cystic fibrosis presents as meconium ileus. Hyperviscid mucosal cell secretions form tarlike meconium in the proximal portion of the intestine and inspissation and obstruction in the distal portion, often resulting in a microcol. The intestinal obstruction requires treatment with enemas, and often with surgery. A child presenting with meconium ileus at birth has an 80% to 90% chance of being diagnosed later with cystic fibrosis.

Rectal prolapse occurs in 3% to 20% of patients with cystic fibrosis. All layers of the rectal wall protrude through the anal sphincter to form a wormlike extrusion, usually easily reducible in infants. The causes are not well-defined, but strong associations with malnutrition, parasitosis, constipation, chronic coughing, Hirschsprung disease, and shigellosis have been found. In some series, up to 11% of infants with rectal prolapse were eventually diagnosed to have cystic fibrosis. Most cases of rectal prolapse with cystic fibrosis respond to pancreatic enzyme replacement therapy.

Do you want to add anything to your Learning Plan?
References:


**American Board of Pediatrics Content Specification(s):**

Understand the diagnosis of cystic fibrosis in newborn infants

Understand the clinical manifestations and pathophysiology of cystic fibrosis in the newborn infant

Understand concept of DNA and mRNA sequence encoding amino acid structure of proteins

Recognize the clinical features associated with autosomal recessive disorders

Understand the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis

Know the relationship between ethnic origin of the parents and risk for specific genetic conditions

Be able to calculate the gene frequency of a disease inherited on a single gene by knowing the population incidence of that disease
Bronchopulmonary dysplasia frequently complicates the course of extremely preterm infants and is associated with neurodevelopmental morbidity. You have met with a 28-year-old primigravida woman and her husband several times to answer questions about prematurity and potential complications while she was being treated for preterm labor. She is at 25 weeks’ gestation. The couple asks you what interventions can prevent or treat some of the complications associated with prematurity, especially those associated with developmental disabilities, such as bronchopulmonary dysplasia and intraventricular hemorrhage.

Of the following, the intervention MOST conclusively proven to reduce the incidence of bronchopulmonary dysplasia is:

1. antenatal corticosteroids
2. high-frequency jet ventilation
3. permissive hypercapnea
4. surfactant
5. vitamin A

You selected 5, the correct answer is 5.

Do you want to add anything to your Learning Plan?
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Bronchopulmonary dysplasia (BPD), also termed chronic lung disease, occurs in about 60% of infants born weighing less than 1,250 g. If mechanical ventilation is needed, the incidence of BPD may be as high as 80%. The pathobiology may include a complex array of interrelated factors such as pulmonary immaturity, surfactant deficiency, prenatal and postnatal infection, oxygen toxicity, ventilator-associated trauma, genetic predisposition, underdeveloped antioxidant defenses, nutritional deficits, and impaired wound healing. BPD is a significant problem because it is associated with postnatal growth failure, chronic pulmonary dysfunction, and developmental disabilities. Therefore, efforts to reduce the incidence of BPD continue to be the focus of intense investigation.

Vitamin A has been conclusively determined to reduce the incidence of BPD in infants born weighing less than 1,000 g. Vitamin A is biologically important for growth and differentiation of epithelial cells. Deficiency of vitamin A and of retinol-binding protein, which occur in extremely low-birthweight infants, is associated with long-term respiratory morbidity. The underlying pathogenic factors responsible for BPD in vitamin A–deficient infants include impaired pulmonary mucus clearance, abnormal water balance across the tracheobronchial epithelium, loss of cilia, abnormal wound healing, and reduced airway distensibility. A meta-analysis of several large, randomized trials of intramuscular vitamin A supplementation (5,000 IU three times per week for 4 weeks) revealed a small (7%), but real reduction in the requirement for supplemental oxygen at 36 weeks’ postmenstrual age (relative risk [RR] = 0.87; 95%
confidence interval \( [CI] = 0.77-0.99 \); number needed to treat \( [NNT] = 15 \). The incidence of BPD (55\%), however, remained high in vitamin A–treated patients.

Antenatal steroids have been proven to reduce mortality \( (RR = 0.62; 95\% CI = 0.51-0.77; NNT = 23) \), respiratory distress syndrome \( (RR = 0.65; 95\% CI = 0.47-0.75; NNT = 12) \), and surfactant use in preterm infants \( (RR = 0.45; 95\% CI = 0.22-0.93; NNT = 9) \). The incidence of BPD has not been reduced with the use of antenatal steroids.

High-frequency ventilation, continuous positive airway pressure, other modes of mechanical ventilation (such as volume-controlled ventilation), respiratory management strategies (such as permissive hypercapnea and gentle ventilation) and inhaled nitric oxide have not been clearly established to reduce the risk of BPD in susceptible infants. High-frequency jet ventilation, when used as the primary mode of mechanical ventilation, has been found to be promising as a mode of ventilation that may reduce the incidence of BPD. In a meta-analysis of two small studies, prophylactic high-frequency jet ventilation reduced the risk of BPD \( (RR = 0.59; 95\% CI = 0.35-0.99) \). However, only 84 infants and 2 trials were included in the meta-analysis, raising concern about overinterpretation of results.

A permissive hypercapnea ventilator management strategy has been hypothesized to reduce the risk of lung injury caused by the volutrauma and barotrauma that contribute to the pathogenesis of BPD. Randomized, controlled trials comparing a permissive hypercapnea strategy to a normocarbia strategy have not demonstrated a significant reduction in the risk of BPD. Post hoc analysis of the largest trial to date found that ventilator support was significantly reduced at 36 weeks' postmenstrual age in the hypercapnea group \( (1\% \text{ vs } 16\%, P<.01) \). However, post hoc analysis is considered a hypothesis-generating exercise and results are most appropriately viewed as unproven because the analysis is not powered to answer the specific question.

Inhaled nitric oxide is a promising treatment that has been found to reduce the incidence of BPD in several randomized trials of preterm infants with respiratory distress syndrome, two of which included multiple institutions. Because the trials were designed differently, assessed short-term outcomes, and had minimal effect on the incidence of BPD, additional research is needed to prove efficacy, determine the specific populations of infants that benefit, and understand the short- and long-term risk-to-benefit ratios. Inhaled nitric oxide was not one of the possible answers in this question.

Surfactant treatment, both prophylactic and therapeutic, is associated with significant improvement in survival, the incidence of respiratory distress syndrome, respiratory morbidity (such as pneumothorax and pulmonary interstitial emphysema), and the composite outcome of BPD or death. Surfactant replacement treatment has not reduced the incidence of BPD alone in preterm infants at less than 30 weeks' gestation.

References:


Biniwale M, Ehrenkranz RA. The role of nutrition in the prevention and management of bronchopulmonary dysplasia. *Semin Perinatol.* 2006;30:200-208


**American Board of Pediatrics Content Specification(s):**

Understand that the requirements for vitamins in newborn infants, and the difference between the preterm infant and the full-term infant

Know the medications, indications for, and complications of drugs used to enhance fetal lung maturity

Understand the prevention of bronchopulmonary dysplasia, chronic lung disease

Understand the management of bronchopulmonary dysplasia/chronic lung disease

Understand the prevention of respiratory distress syndrome

Understand the risks and effects of high-frequency ventilation
A 2.9-kg term newborn male infant is admitted to the neonatal intensive care unit for respiratory distress and cyanosis. Pregnancy was marked by lack of prenatal care. Delivery was vaginal and spontaneous. There was no meconium staining of the amniotic fluid. Apgar scores were 8 and 8 at 1 and 5 minutes, respectively. A chest radiograph obtained shortly after admission is depicted in Figure 1.

**Figure 1**

Oxygen saturation probes located on his right hand and right foot reveal readings of 93% and 81%, respectively.

Of the following, the MOST likely diagnosis for the infant in the vignette is:

1. congenital cystic adenomatoid malformation
2. congenital diaphragmatic hernia
3. neuroblastoma
4. pulmonary sequestration
5. tension pneumothorax

You selected 1., the correct answer is 1.

The radiographic findings in the infant in this vignette are consistent with the diagnosis of congenital cystic adenomatoid malformation (CCAM). CCAM is a hamartomatous lesion composed of cystic and adenomatous overgrowth of terminal bronchioles that is thought to result from failure of normal bronchoalveolar differentiation during the pseudoglandular stage of lung development. The different types of CCAMs are thought to originate at different levels of the tracheobronchial tree.
1. Type I CCAM contains one or more cysts measuring more than 2 cm in diameter, surrounded by multiple smaller cysts. The cysts are lined by ciliated columnar epithelium and their walls contain abundant elastic tissue. Type I CCAM is the most common type, constituting approximately 70% of cases.

2. Type II CCAM contains cysts measuring up to 2 cm in diameter. These cysts are lined by cuboidal or columnar epithelium and resemble dilated bronchioles.

3. Type III CCAM usually contains cysts less than 0.5 cm in diameter and are lined by cuboidal epithelium.

Blood flow to CCAMs originates from the pulmonary arterial circulation. The presentation of CCAM is variable. Many of these lesions are identified on routine prenatal ultrasonography. Other CCAMs are identified on chest radiographs obtained because of clinical symptoms or as incidental findings in asymptomatic infants who have chest images taken for other reasons. In general, the likelihood of respiratory distress and its severity increases with the size of the lesion. Typical signs include tachypnea, increased respiratory effort with grunting and retractions, and cyanosis. Air trapping caused by restrictive connections to the tracheobronchial tree and expansion of cysts may lead to progressive worsening of respiratory distress. Large lesions can compromise alveolar growth and development by compressing adjacent normal tissue; single or multiple large cysts can result in lung hypoplasia and concomitant persistent pulmonary hypertension of the newborn. Large CCAMs that shift the mediastinum may obstruct the inferior vena cava and compress the heart, resulting in an increase in central venous pressure and hydrops (Figure 1).

Figure 1: Congenital cystic adenomatoid malformation

Congenital diaphragmatic hernia (CDH) is a developmental defect in the diaphragm that allows abdominal viscera to herniate into the chest (Figure 2).

Figure 2: Congenital diaphragmatic hernia

Affected neonates usually present during the first few hours after birth with respiratory distress that may be mild or so severe as to be incompatible with life. During embryogenesis, the diaphragm develops anteriorly as a septum between the heart and liver. The final closure occurs at the left foramen of Bochdalek between 8 and 10 weeks of gestation. At 10 weeks, the bowel returns from the yolk sac to the abdominal cavity. If the bowel enters the abdominal cavity before the foramen close, herniation of abdominal contents into the thorax may occur.
Because the herniation coincides with critical periods of lung development, lung compression by the herniated bowel results in pulmonary hypoplasia. In most cases of CDH, herniation occurs on the left. Right-sided diaphragmatic hernia occurs in 11% and bilateral herniation in 2% of cases (Figure 2).

Neuroblastomas are derived from undifferentiated neural crest cells that differentiate into the sympathetic nervous system. The primary locations of neuroblastoma correspond to the locations of the sympathetic chain: adrenal medulla, retroperitoneum, pelvis, mediastinum, or extracranial craniofacial space. Children with thoracic tumors (14% of cases) may have an abnormal mediastinal mass on incidental chest radiography, or present with dysphagia, cough, and respiratory distress. The mass is solid, not cystic, and located close to the mediastinum (Figure 3).

![Figure 3: Neuroblastoma](image)

Pulmonary sequestration (PS) is defined as an area of nonfunctioning lung tissue that receives its blood supply from the systemic circulation and does not communicate with the tracheobronchial tree. Two classic forms of PS have been described: extralobar (ELPS) and intralobar (ILPS). ELPS is an entirely separate segment of lung tissue and typically found in the costophrenic sulcus of the left side of the chest. ELPS may also be located in the mediastinum, pericardium, or within or below the diaphragm. ILPS accounts for 75% of PS and are usually located in the posterobasal portion of the lower lobes. Infants may present with symptoms determined by the location of the sequestration, such as respiratory distress or feeding difficulties, or ILPS may be detected as an incidental prenatal or postnatal imaging finding. On chest radiograph, pulmonary sequestration usually appears as a well-defined, solid, retrocardiac mass in the cardiophrenic angle (Figure 4).

![Figure 4: Pulmonary sequestration](image)

A tension pneumothorax results from any lung parenchymal or bronchial injury that acts as a one-way valve. Air moves into the pleural space but cannot exit. As pressure within the intrapleural space builds, the heart and mediastinal structures are pushed to the contralateral side. The mediastinum impinges on and compresses the contralateral lung. Hypoxia results because collapse of the lung on the affected side and compression of the lung on the contralateral side compromise gas exchange. Clinical symptoms include tachypnea, grunting, pallor, or cyanosis. In unilateral pneumothorax, the mediastinum may be shifted away from the affected side, and breath sounds may be diminished compared with the affected side. A large tension pneumothorax is readily diagnosed by the presence of air in the pleural cavity.
separating the parietal and visceral pleura, collapse of the ipsilateral lobes, displacement of the mediastinum to the contralateral side, and flattening of the diaphragm (Figure 5).

Figure 5: Tension pneumothorax

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


Stanton M, Davenport M. Management of congenital lung lesions. Early Hum Dev. 2006;82:289

American Board of Pediatrics Content Specification(s):

Understand the stages of normal and abnormal cellular development of all components of the lung

Recognize the clinical features of extrapulmonary causes of respiratory distress, including diaphragmatic hernia, diaphragmatic paralysis, and cord transection

Recognize the clinical features of congenital malformations of the lung, including congenital pulmonary lymphangiectasia, the cystic lung diseases such as congenital lobar emphysema, cystic adenomatoid malformation, and mediastinal tumors

Recognize the radiographic features of congenital malformations of the lung, including congenital pulmonary lymphangiectasia, the cystic lung diseases such as congenital lobar
emphysema, cystic adenomatoid malformation, and mediastinal tumors

Understand the pathophysiology of air leaks

Recognize the radiographic features of air leaks
A 3,200-g male infant is born to a 28-year-old primiparous woman at an estimated gestational age of 37 weeks. The pregnancy was complicated by right-sided fetal pleural effusion, first detected with ultrasonography at 30 weeks' gestation. After delivery, the infant's resuscitation includes thoracentesis that yields 90 mL of amber fluid from the right side of the chest. The infant has no dysmorphic features, generalized edema, or evidence of hemolysis. The pleural fluid reveals the following: nucleated cell count, 560 cells/μL (560×10⁶ cells/L) with a differential count of 93% lymphocytes, 5% neutrophils, and 2% monocytes; glucose, 62 mg/dL (3.4 mmol/L); protein, 2.8 g/dL (28 g/L); triglyceride, 3.0 mg/dL (0.03 mmol/L); cholesterol, 50 mg/dL (1.3 mmol/L); and lactate dehydrogenase, 90 U/L (1.5 μkat/L). The pleural fluid is sent for bacterial and viral culture.

Of the following, the MOST likely cause of pleural effusion in this infant is:

1. congenital chylothorax
2. heart failure
3. iatrogenic extravasation
4. intrauterine infection
5. mediastinal malignancy

You selected 3, the correct answer is 1.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Congenital chylothorax, accumulation of chyle-containing lymphatic fluid in the pleural space, is the most common cause of pleural effusion that manifests during the fetal and early neonatal periods, as in the infant in this vignette. Its incidence is estimated at 1 in 6,000 to 10,000 live births; it is twice as common in males as in females. The effusion is usually unilateral with a right-sided preponderance. Congenital chylothorax may be transient and resolves spontaneously when it results from a potentially reversible obstruction or hypoplasia of the thoracic duct. Conversely, congenital chylothorax may be persistent and does not resolve spontaneously when it results from an intrinsic abnormality of the lymphatic system in the form of lymphangiomatosis or lymphangiectasia. The former represents sequestered lymphatic tissue in solitary or multifocal lesions; the latter represents distention of pulmonary subpleural and interlobular lymphatics. Persistent congenital chylothorax often is associated with other congenital malformations such as tracheoesophageal fistula and congenital heart defects; syndromes such as Noonan syndrome, Turner syndrome, and Down syndrome; and pulmonary abnormalities such as sequestration and congenital cystic adenomatoid malformation.
The analysis of pleural fluid is helpful in the diagnosis of congenital chylothorax. The fluid, in the absence of enteral feeding, typically is amber colored, is rich in lymphocytes (differential count >70%), and may not show an elevated triglyceride concentration. With enteral feeding, especially using milk rich in long-chain triglycerides, the pleural fluid becomes milky in appearance, remains rich in lymphocytes, and shows an elevated triglyceride concentration (>110 mg/dL [1.2 mmol/L]). The evolution of pleural effusion in the infant in this vignette, its manifestation at birth before any postnatal interventions, and the pleural fluid analysis are compatible with the diagnosis of congenital chylothorax.

Pleural effusion resulting from heart failure often is bilateral and accompanied by hydrops. Hydrops fetalis may be associated with congenital structural heart malformations and abnormalities of cardiac rhythm. The structural malformations typically include hypoplastic left heart syndrome and endocardial cushion defect. Among the rhythm abnormalities, tachyarrhythmias, including supraventricular tachycardia and atrial flutter, are more common than bradyarrhythmias such as heart block. The severity and unilateral localization of the pleural effusion as well as the absence of generalized edema make heart failure an unlikely cause of pleural effusion in the infant in this vignette.

Extravasation of fluid into the pleural space can result from injury to the thoracic duct, or obstruction of the subclavian vein or superior vena cava. Surgical procedures, such as correction of coarctation of aorta, ligation of patent ductus arteriosus, and repair of congenital diaphragmatic hernia, may cause inadvertent injury to the thoracic duct. The thrombosis of the subclavian vein or superior vena cava and resultant increase in central venous pressure may cause extravasation of fluid into the pleural space. The thrombosis often is a complication of long-term use of indwelling catheters for administration of parenteral nutrition. The absence of any of these interventions makes iatrogenic extravasation an unlikely cause of pleural effusion in the infant in this vignette.

Pneumonia resulting from perinatally acquired bacterial infection involving organisms such as group B Streptococcus may be associated with pleural effusion. Typically, the effusion is bilateral, less voluminous than that described in this vignette, and characterized by neutrophilic preponderance. Rarely, in extreme cases of late-onset bacterial sepsis, the pneumonia may be complicated by a localized collection of pus as in lung abscess or empyema. The nature of the pleural fluid and the absence of features suggestive of sepsis make intrauterine infection an unlikely cause of pleural effusion in the infant in this vignette.

Mediastinal malignancies, such as lymphoma, sarcoma, or neuroblastoma, are rare causes of pleural effusion in neonates. The effusion in such cases may result from obstruction and rupture of the lymphatics induced by the tumor, or from invasion of the lymphatics by the tumor.

References:


Dubin PJ, King IN, Gallagher PG. Congenital chylothorax. *Curr Opin Pediatr.*

**American Board of Pediatrics Content Specification(s):**

Understand the pathophysiology and recognize the clinical, radiographic, and laboratory manifestations of hydrothorax/chylothorax
A 6-month-old male infant born at 27 weeks' gestation is being discharged home. It is January. He has bronchopulmonary dysplasia requiring supplemental oxygen and diuretics, a small ventricular septal defect, and feeding incoordination. Gavage feeding of a high-caloric formula is being continued. A 19-year-old sibling who smokes cigarettes will be caring for the infant while his parents work. You have counseled the family members, including the sibling, about common infections and their prevention, immunizations, and the risks of exposure to tobacco smoke and environmental pollutants.

Of the following, the risk factor MOST associated with hospitalization for respiratory syncytial virus (RSV)–associated bronchiolitis in the infant in this vignette is:

1. bronchopulmonary dysplasia
2. formula feeding
3. teenage sibling
4. tobacco-smoke exposure
5. ventricular septal defect

You selected 1, the correct answer is 1.

Do you want to add anything to your Learning Plan?
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Bronchiolitis is a common lower respiratory tract infection that affects nearly all infants by the time they are 2 years old. In the United States, 20% of infants younger than 1 year old are seen in a clinic or emergency department, or are hospitalized (3%) for bronchiolitis. More than 120,000 hospitalizations and 450 deaths annually are attributed to bronchiolitis. Although two-thirds of the infants who die of bronchiolitis are born at term, high-risk populations include infants born prematurely or who have chronic lung disease, significant congenital heart disease, neurologic disorders, or immunodeficiency. Bronchiolitis has been associated with recurrent wheezing in early childhood. About 40% of infants hospitalized for bronchiolitis during their first year after birth have recurrent wheezing compared with 20% of infants without bronchiolitis. It is not clear whether the association between bronchiolitis and later wheezing is causal or a marker for genetic predisposition and limited respiratory reserve.

Respiratory syncytial virus accounts for two-thirds of bronchiolitis cases. Human metapneumovirus accounts for 3% to 12% of cases, and may occur together with RSV. Influenza, parainfluenza, rhinoviruses, and adenoviruses account for most of the remaining cases.

Respiratory syncytial virus is responsible for annual epidemics of infant and childhood respiratory disorders throughout the world. In the central United States, the RSV season typically begins in November, peaks between December and February, and ends in April (Figure). Regional and annual variations in the timing of the RSV season frequently exist.
Palivizumab, a humanized monoclonal antibody directed against the highly conserved F glycoprotein found on the surface of RSV, has become an important prophylactic measure to prevent severe RSV in high-risk infants. The presence of bronchopulmonary dysplasia, as in the infant in the vignette, prematurity, and congenital heart disease are the most significant high-risk factors for severe RSV infection. Palivizumab was found in large randomized trials of high-risk infants to reduce the severity of RSV infection. Severity of RSV disease in these trials was defined by rates of admission to a hospital or an intensive care unit, respiratory severity scores, length of hospitalization, and duration of supplemental oxygen use, all of which were reduced with palivizumab.

High-risk populations who are candidates for palivizumab prophylaxis during the RSV season are listed in the Table.
For infants younger than 6 months old who are born at 33 to 35 weeks’ gestation, two risk factors are required because none of these factors alone increases the risk of hospitalization substantially. Notice that exposure to tobacco smoke is not included as a risk factor. The arguments to omit recurring exposure to tobacco smoke stem from inconsistent associations in epidemiologic studies and the belief that exposure can be controlled by the family less expensively than giving monthly intramuscular injections of palivizumab. Carroll and colleagues recently described a significant association of maternal smoking and bronchiolitis in a large population-based retrospective cohort study of term infants. These findings provide more convincing evidence for the risk of passive tobacco smoke exposure to infants, even those born at term without predisposing risk factors.

Palivizumab prophylaxis has not been studied in immunocompromised children or those with cystic fibrosis, but strong theoretical support exists. Prophylaxis, therefore, should be individualized. Prophylaxis of hospitalized patients, especially those at high risk, to control hospital-acquired RSV has not been proven effective. Strict handwashing procedures, contact isolation, and supportive treatment should be emphasized if an infant acquires RSV while hospitalized. Palivizumab is not an effective treatment for acute infections.

Term and preterm infants born at 33 to 35 weeks’ gestation without risk factors account for most cases of RSV during infancy and early childhood. Palivizumab has not proven cost effective in these populations and an effective vaccine has not been available. Parents and caregivers may prevent RSV infections by careful handwashing and limiting exposure to infected children and people, especially in crowded locations such as child care centers. Breast milk feeding is encouraged because immune function (RSV-specific antibody and lactoferrin) may be enhanced. The risk of severe RSV disease during the first 5 months after birth is significantly increased in infants fed formula rather than breast milk.

**Table: Criteria for Palivizumab Prophylaxis During Respiratory Syncytial Virus (RSV) Season**

<table>
<thead>
<tr>
<th>Age</th>
<th>Gestational Age</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 mo</td>
<td>&lt;28 wk</td>
<td>Bronchopulmonary dysplasia during the 6 months before the next RSV season.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Definition of Bronchopulmonary Dysplasia:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supplemental oxygen, bronchodilator, diuretic, or corticosteroid</td>
</tr>
<tr>
<td>&lt;12 mo</td>
<td>29-32 wk</td>
<td>2 of the following risk factors:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Child care attendance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- School-age siblings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Exposure to environmental air pollution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Congenital abnormalities of the airways</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Severe neuromuscular disease</td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>33-35 wk</td>
<td>Hemodynamically significant congenital heart disease (not present in the infant in the vignette) defined as those infants with:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Congestive heart failure and receiving medications for control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Moderate to severe pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cyanotic heart disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Surgical procedures requiring cardiopulmonary bypass (redosing is recommended)</td>
</tr>
</tbody>
</table>

Do you want to add anything to your Learning Plan?
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References:

Black CP. Systematic review of the biology and medical management of respiratory syncytial virus infection. Respir Care. 2003;43(3):209-233


Smyth RL, Openshaw PJM. Bronchiolitis. Lancet. 2006;368:312-322


Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. J Pediatr. 2003;143:S112-S117

American Board of Pediatrics Content Specification(s):

Understand the epidemiology, pathogenesis, and prevention of neonatal infections with respiratory syncytial virus

Understand the treatment of neonatal infections with respiratory syncytial virus

Understand the complications of neonatal infections with respiratory syncytial virus
March: Question 4

A mother was undergoing repeat cesarean section at 38 weeks' gestation under general anesthesia. In the delivery room, the infant needed endotracheal intubation for assisted ventilation. The endotracheal tube was placed successfully with the tip in the suprasternal notch after three initial failed attempts at intubation. In the neonatal intensive care unit, the infant showed sustained spontaneous respirations by 15 minutes after birth, and underwent extubation. The next day, the infant was doing well and started to breastfeed. On auscultation of the chest, however, you noted mild biphasic stridor.

Of the following, the anatomical area of the respiratory tract MOST likely to produce the stridor is:

1. anterior nasal
2. choanal
3. laryngeal
4. subglottic
5. tracheal

You selected 4, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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Stridor occurs when a narrowed portion of the airway yields turbulence in the air flow. In general, biphasic stridor results from narrowing in the subglottic region and is usually not accompanied by voice abnormalities. Inspiratory stridor accompanies narrowing at the laryngeal or vocal cord level, whereas expiratory stridor suggests an intrathoracic condition.

Subglottic stenosis is defined as an airway diameter smaller than 4 mm in the term infant and smaller than 3 mm in the preterm infant. Subglottic stenosis may be acute and acquired, as suggested by the infant in this vignette, who underwent multiple attempts at intubation. The airway is surrounded by the cricoid cartilage. The cricoid is the only fixed ring of cartilage, and mucosal edema easily may cause transient obstruction at this level. Subglottic stenosis occurs in about 8% of infants who require prolonged intubation. Factors increasing the risk of subglottic stenosis include duration of intubation, endotracheal tube size and motion, and number of intubations. For severe subglottic stenosis, especially if associated with an inability to extubate, anterior cricoid split or tracheostomy may be required.

Subglottic stenosis may be congenital, caused by either membranous or cartilaginous tissue, resulting in bilateral or circumferential narrowing in the subglottic region. Stridor, present at birth, may worsen with time. Subglottic stenosis also may be the result of subglottic hemangioma, which, along with bilateral vocal cord paralysis, constitutes potentially life-threatening forms of congenital stridor. In such cases, stridor is not noted initially, but becomes evident and progressively increases over a
few months. One half of children with subglottic hemangioma have a raised, erythematous birthmark (cutaneous hemangioma) on the chest. The hemangiomata gradually enlarge through the first year and involute thereafter. Subglottic cysts have been reported after intubation. These cysts have a delayed onset of symptoms (1 to 2 months after extubation) and may cause progressive stridor. Diagnostic techniques for subglottic stenosis include microlaryngoscopy and/or bronchoscopy. Some cases require intervention, including laser excision, steroids, interferon-alpha 2a administration, or cricoid split, or tracheostomy.

Blockage of the airway at the anterior nasal level, which could occur from prolonged irritation of nasal mucosa with subsequent scarring, or at the choanal level, would not be expected to produce stridor. Neonates with nasal obstruction often present with cyanosis when quiet, which is relieved by crying, because infants are often obligate nose-breathers. Congenital nasal obstruction may occur because of nasal pyriform aperture stenosis or deviated septum, or it can be due to gliomas and encephaloceles. Choanal blockage may be relieved by using an oral airway pending anatomic confirmation with computed tomography and definitive treatment by an otolaryngologist.

Inspiratory stridor reflects obstruction at the laryngeal level, at or above the level of the vocal cords. Laryngomalacia is the most common form of congenital stridor—representing 70% to 80% of cases. Characterized by an intermittent, whooping-type, late inspiratory stridor with little or no associated distress, laryngomalacia is generally benign and resolves in 90% of patients by 1½ years of age. However, some infants, like those with congenital subglottic stenosis, will become more symptomatic during the first months after birth. A few patients (<5%) require epiglottoplasty or tracheostomy.

Inspiratory stridor also may result from unilateral or bilateral vocal cord paralysis, the second most common cause of stridor. Bilateral vocal cord paralysis may be associated with a weak cry accompanied by retractions and/or cyanosis. The retractions increase with agitation, and feeding difficulty may result in failure to thrive. The condition may be life-threatening. Unilateral vocal cord paralysis usually is not associated with respiratory distress, but may result in hoarseness or a breathy voice in later life. Diagnosis is made by means of flexible upper airway endoscopy. Unilateral vocal cord paralysis seldom requires treatment. Bilateral vocal cord paralysis requires search for associated central nervous system disease. If the Arnold-Chiari anomaly is present, surgical decompression may result in resolution of the cord paralysis. In other cases, tracheostomy followed by vocal cord lateralization may be needed unless the condition resolves spontaneously.

Due to a failure of the posterior larynx and/or cricoid to fuse, laryngeal cleft may have associated stridor depending on the degree of associated subglottic narrowing and/or redundant supraglottic tissue. Recurrent respiratory symptoms or infection associated with aspiration, difficult swallowing, and choking suggest this rare condition. Microlaryngoscopy or bronchoscopy can be used to confirm the diagnosis; aspiration may be found on contrast swallow study. Repair is done surgically.

Expiratory stridor reflects intrathoracic airway turbulence, as would be found with tracheomalacia, its most common cause. Tracheomalacia may be present at birth. Most cases gradually improve and require no intervention, but some cases are associated with various vascular anomalies. Tracheal or bronchial webs may also create expiratory stridor. An aberrant innominate artery may compress the anterior trachea. Double aortic arch or other vascular rings may impinge on the trachea and the esophagus. Unilateral bronchomalacia or impingement on only one bronchus may produce expiratory stridor associated with unilateral air-trapping on chest radiography. The various causes of expiratory stridor can be diagnosed by means of techniques such as chest radiography, bronchoscopy, fluoroscopy, contrast esophography,
magnetic resonance imaging, and computed tomography. Treatment of tracheomalacia includes observation, mucolytics, continuous positive airway pressure, and tracheostomy. Webs and stenoses are ruptured, dilated, or resected. Treatment of impingements depends on the specific condition and its anatomic structure.

References:


American Board of Pediatrics Content Specification(s):

Know the complications of tracheal intubation, including subglottic stenosis

Know the various causes of stridor in the newborn

Identify the potential complications of airway management in the delivery room and know their management

Understand the factors that affect airway resistance and how resistance changes with various lung disorders

Know the factors that influence upper airway patency

Understand the clinical features of an infant with airway obstruction, such as vascular rings, choanal atresia, and tracheal abnormalities

Plan appropriate management for an infant with airway obstruction, such as vascular rings, choanal atresia, and tracheal abnormalities
You are asked to evaluate a 9-hour-old male infant with tachypnea. He was delivered by cesarean birth to a 24-year-old white mother at 38 0/7 weeks' gestation. She had a history of frequent outbreaks of genital herpes before pregnancy and had a vaginal lesion at the time of delivery. Her group B Streptococcus status is not known. Her membranes ruptured 1 hour before delivery and the amniotic fluid was meconium stained. She was not in labor. The infant cried immediately after birth and had Apgar scores of 8 and 9 at 1 and at 5 minutes, respectively. He became tachypneic 3 hours after birth after an initial attempt at breastfeeding. When you examine him he has a respiratory rate of 100 breaths per minute. In 30% humidified oxygen from a nasal cannula, he is able to maintain his oxygen saturation above 95%. He has a few subcostal retractions, mild nasal flaring, and an occasional grunt when he is disturbed.

Laboratory results are as follows:

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Patient Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count, /μL (×10^9/L)</td>
<td>14,000 (14)</td>
</tr>
<tr>
<td><strong>Differential</strong></td>
<td></td>
</tr>
<tr>
<td>Band, %</td>
<td>2</td>
</tr>
<tr>
<td>Segmented neutrophils, %</td>
<td>64</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>26</td>
</tr>
<tr>
<td>Monocytes, %</td>
<td>8</td>
</tr>
<tr>
<td>Platelet count, ×10^9/μL (×10^9/L)</td>
<td>230 (250)</td>
</tr>
<tr>
<td><strong>Capillary blood gas</strong></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.29</td>
</tr>
<tr>
<td>PCO₂, mm Hg</td>
<td>58</td>
</tr>
<tr>
<td>PO₂, mm Hg</td>
<td>35</td>
</tr>
</tbody>
</table>

The infant's initial chest radiograph is shown in the Figure.

Of the following, the MOST effective treatment to reduce the risk of respiratory distress in this neonate would be:

- chest physiotherapy immediately after delivery
Respiratory distress is one of the most frequent reasons for admission of term and late preterm neonates to an intensive care unit. Causes of respiratory distress in the term infant may be pulmonary or nonpulmonary (Table).

<table>
<thead>
<tr>
<th>Table: Potential Pulmonary Causes for Respiratory Distress in Term Neonates*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenchymal conditions:</strong></td>
</tr>
<tr>
<td>• Transient tachypnea of the newborn</td>
</tr>
<tr>
<td>• Meconium aspiration syndrome and other aspirations</td>
</tr>
<tr>
<td>• Respiratory distress syndrome</td>
</tr>
<tr>
<td>• Pneumonia</td>
</tr>
<tr>
<td>• Pulmonary edema</td>
</tr>
<tr>
<td>• Pulmonary hemorrhage</td>
</tr>
<tr>
<td>• Pulmonary lymphangioedema</td>
</tr>
<tr>
<td><strong>Developmental abnormalities:</strong></td>
</tr>
<tr>
<td>• Lobar emphysema</td>
</tr>
<tr>
<td>• Pulmonary sequestration</td>
</tr>
<tr>
<td>• Cystic adenomatoid malformation</td>
</tr>
<tr>
<td>• Congenital diaphragmatic hernia</td>
</tr>
<tr>
<td>• Tracheoesophageal fistula</td>
</tr>
<tr>
<td>• Pulmonary hypoplasia</td>
</tr>
<tr>
<td><strong>Airway abnormalities:</strong></td>
</tr>
<tr>
<td>• Choanal atresia/stenosis</td>
</tr>
<tr>
<td>• Laryngeal web</td>
</tr>
<tr>
<td>• Laryngotracheomalacia or bronchomalacia</td>
</tr>
<tr>
<td>• Subglottic stenosis</td>
</tr>
<tr>
<td><strong>Mechanical abnormalities:</strong></td>
</tr>
<tr>
<td>• Rib cage anomalies</td>
</tr>
<tr>
<td>• Pneumothorax</td>
</tr>
<tr>
<td>• Pneumomediastinum</td>
</tr>
<tr>
<td>• Pleural effusion</td>
</tr>
<tr>
<td>• Chylothorax</td>
</tr>
</tbody>
</table>

* Adapted from Fidel-Rimon and Shinwell (2003).

Bacterial or viral pneumonia, respiratory distress syndrome (RDS), meconium aspiration, and transient tachypnea of the newborn (TTN) are common pulmonary causes of respiratory distress in the late preterm and term neonate. The neonate in the vignette has TTN. TTN or “wet lung” is a self-limited disorder generally affecting neonates born at or near term. It occurs in approximately 11 in 1,000 live births and is far more common in neonates born via cesarean section, especially those without labor. Affected neonates with TTN usually present within the first 6 hours after birth with tachypnea and have milder symptoms of respiratory distress than neonates with RDS or pneumonia. Symptoms may include:

- cyanosis
- subcostal retractions
nasal flaring
increased anteroposterior diameter of the chest
expiratory grunting
tachypnea

Arterial blood gases may show respiratory acidosis, secondary to air trapping, and hypoxemia. The complete blood count is normal. The chest radiograph and hospital course are usually key to making the diagnosis of TTN. Early radiographic findings may include:

- prominent perihilar streaking
- mild to moderate cardiomegaly
- fluffy densities
- fluid in the minor fissure
- pleural effusions
- hyperinflation with flattening of the diaphragm

Signs and symptoms usually are transient and last for 12 to 24 hours in mild cases and 48 to 72 hours in severe cases.

For effective gas exchange to occur, the alveolar spaces must be cleared of excess fluid. The exact mechanism for clearance of fetal alveolar fluid is still unknown. The expulsion of lung fluid during the "vaginal squeeze" at delivery accounts for only a fraction of lung fluid clearance. Sodium transport is an important mechanism for transepithelial movement of alveolar fluid into the interstitium of the lung where it is subsequently absorbed into the vasculature. Neonates with TTN are more likely to have immature transepithelial sodium transport. High levels of endogenous catecholamines present during labor and at birth are important physiologic regulators of sodium movement across the pulmonary epithelium.

Treatment of TTN is supportive, because symptoms resolve with time. Supplemental oxygen may be required to maintain adequate oxygen saturation. Continuous positive airway pressure or mechanical ventilation is rarely required. Neither chest physiotherapy nor diuretics have been shown to be effective in clearing fluid from the lungs of neonates with TTN.

Herpes simplex virus is a common viral sexually transmitted disease in the United States. Five percent to 10% of women have symptomatic recurrent herpes during their pregnancy, of whom 25% will have an outbreak during the last month of their pregnancy. Because a majority of neonatal herpes results from transmission near delivery, preventive strategies have focused on the peripartum period. Current guidelines recommend a cesarean delivery for all women with active genital herpes lesions or prodromal symptoms at the time of presentation in labor.

Valacyclovir, a prodrug of acyclovir, was developed to improve bioavailability of acyclovir by enhancing absorption from the gastrointestinal tract. A randomized trial has shown that in women with a history of recurrent genital herpes valacyclovir treatment after 36 weeks' gestation reduces herpes simplex virus shedding, recurrent genital herpes, and cesarean delivery (4% in the valacyclovir group and 13% in the placebo group [P = .009]).

Neonates delivered vaginally after labor have the lowest risk of developing TTN. If the mother in the vignette had received valacyclovir treatment beginning at 36 weeks' gestation, her risk of having a herpes outbreak and a cesarean delivery would have been reduced. Thus the risk of TTN in her newborn would be lower.

Antenatal glucocorticosteroid treatment is an established means of reducing the risk of RDS in preterm neonates. The infant does not have clinical or radiographic findings of RDS and the 1994 National Institutes of Health consensus panel guidelines do not recommend antenatal glucocorticosteroids for women beyond 34 weeks' gestational age.

The use of antenatal glucocorticosteroids for the prevention of TTN after an elective cesarean birth is being investigated. A recent pilot study evaluating the efficacy of betamethasone in preventing respiratory distress in neonates delivered by an elective cesarean section suggested
that two doses of bethamethasone 48 hours before delivery could significantly decrease admissions to the NICU for respiratory distress. Until larger randomized trials are completed, antenatal glucocorticosteroid therapy cannot be recommended to prevent TTN.

Intrapartum intravenous penicillin effectively reduces the risk of group B streptococcal disease among newborns born to women with group B streptococcal vaginal colonization; however, penicillin treatment is required in women whose streptococcal status is unknown only if they deliver before 37 weeks’ gestational age, have ruptured membranes for at least 18 hours, or have an intrapartum fever. The mother in the vignette has none of these risk factors. Clinical, laboratory, and radiographic findings of the neonate in the vignette are not compatible with a diagnosis of group B streptococcal pneumonia or septicemia. Intrapartum intravenous penicillin does not prevent TTN.

Passage of meconium in utero occurs in 8% to 20% of all deliveries and meconium aspiration syndrome occurs in about 1% to 4% of deliveries complicated by meconium stained fluid. Resuscitation of neonates born to mothers with meconium-stained fluid is based on their presentation after delivery. Neonates who are not vigorous, as defined by poor respiratory effort, poor muscle tone, and a heart rate less than 100 beats per minute should have their trachea suctioned immediately after delivery. If the infant is vigorous, tracheal suctioning is not required. The neonate in the vignette was vigorous at birth and would not require tracheal suctioning at birth. Clinical, laboratory, and radiographic findings of the neonate in the vignette are not consistent with meconium aspiration syndrome.

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References:


Jain L, Dudell GG. Respiratory transition in infants delivered by cesarean section. Semin Perinatol. 2006;30:296-304


American Board of Pediatrics Content Specification(s):

Recognize the clinical, laboratory, radiographic, and pathologic features of transient tachypnea
of the newborn infant

Determine the prevention and management of transient tachypnea of the newborn infant
A 3-week-old term male infant is readmitted for tachypnea and subcostal retractions. His initial birth hospitalization was complicated by transient respiratory distress associated with group B streptococcal sepsis; a small right-sided pleural effusion was present on a chest radiograph. Otherwise, the infant was asymptomatic and he was discharged from the hospital 2 weeks after birth.

Of the following, the MOST likely associated respiratory abnormality in this infant is a:

1. cystic adenomatoid malformation
2. diaphragmatic hernia
3. lobar emphysema
4. pulmonary lymphangiectasis
5. pulmonary sequestration

You selected 3, the correct answer is 2.

Neonatal group B streptococcal sepsis (GBS) is associated with late-presenting congenital diaphragmatic hernia, as in the infant in the vignette. The diaphragmatic hernia is located on the right in more than 90% of reported cases and is frequently preceded by a right pleural effusion. Symptoms at presentation are usually respiratory with acute respiratory deterioration found in most cases. Nearly two thirds of cases involve male infants, as in patients presenting with early diaphragmatic hernia, and the median gestational age at birth is 37 weeks. Survival after surgical repair is 90%.

The explanation for the association between GBS and late-presenting right diaphragmatic hernia is speculative. One hypothesis associates pneumonia and infection with diaphragm necrosis and rupture; however, diaphragmatic hernia has not been reported with other pathogens. Another hypothesis suggests that positive pressure ventilation, which is required in some cases of GBS, increased intrathoracic pressure, and noncompliant stiff lungs resulting from pneumonia prevent right-sided herniation of liver and intestine initially after birth.

Infection, specifically GBS, has not been associated with cystic adenomatoid malformation of the lung, lobar emphysema, pulmonary sequestration, or pulmonary lymphangiectasis. Cystic adenomatoid malformation of the lung is a hamartomatous change in the terminal bronchioles of the lung resulting in microcystic and macrocystic masses; although presentation is often at birth, small lesions may not cause symptoms and are incidentally discovered.
Lobar emphysema is a pathologic overinflation affecting one lobe of the lung that is caused by intrinsic and extrinsic factors; presentation after the perinatal period, like that found with GBS-associated diaphragmatic hernia, occurs in about half the cases.

Congenital pulmonary lymphangiectasis is a rare form of lymphatic obstruction isolated to the lung. If not associated with congenital heart disease and not extensive, presentation may occur weeks to months after birth. Pulmonary sequestration, characterized as an accessory segment of lung tissue with vascular supply originating from the aorta, is most often discovered incidentally in children and young adults who have had recurrent pneumonia.

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References:


Rescorla FJ, Yoder MC, West KW, Grosfeld JL. Delayed presentation of a right-sided diaphragmatic hernia and group B streptococcal sepsis: two case reports and a review of the literature. Arch Surg. 1989;124(9):1083-1086


American Board of Pediatrics Content Specification(s):

Understand the complications of group B streptococcal infections

Recognize the clinical features of extrapulmonary causes of respiratory distress, including diaphragmatic hernia, diaphragmatic paralysis, and cord transaction

Recognize the clinical features of congenital malformations of the lung, including congenital pulmonary lymphangiectasis, the cystic lung diseases, such as congenital lobar emphysema, cystic adenomatoid malformation, and mediastinal tumors
A 30-week-gestation infant is born precipitously and has respiratory distress at 30 minutes of age. You suspect the respiratory distress syndrome of prematurity, and obtain a chest radiograph (Figure).

Figure: Chest radiograph of a newborn with respiratory distress syndrome. Note the ground-glass appearance to the lung-fields. Arrows point to air bronchograms (from AAP PREP Self-Assessment, Item 238A, courtesy of Brian Carter, MD)

You note air bronchograms (arrows) and a ground-glass appearance of the lung-fields on the radiograph.

Of the following, the basic gas law that BEST explains the ground-glass appearance is the law of:

- [ ] Boyle
- [x] Charles
- [ ] Dalton
- [ ] Laplace
- [ ] Poiseuille

You selected [x], the correct answer is [1].

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The basic gas laws are useful to understand respiratory physiology. Boyle’s law relates gas...
pressure and volume. Charles's law relates volume and temperature. Dalton's law relates the partial pressures in a gas mixture to the total pressure. Poiseuille's law relates gas flow through a tube to the tube radius. Laplace's law relates pressure to surface tension and radius of curvature. Of these, Laplace's law applied to the small airways of the neonatal lung best explains the microatelectasis that produces the ground-glass appearance of the respiratory distress syndrome on chest radiography.

Laplace's law states that the gas pressure in a circumscribed volume increases directly with the surface tension at the gas-fluid interface, and inversely with the radius of curvature. As a mammalian lung deflates, the small airways collapse before the alveoli. A small airway with a high surface tension pulling on its surface will close at a higher air pressure than a similar small airway with a low surface tension, as expected by the Laplace law.

Pulmonary surfactant serves to lower the surface tension of small airways and keep them patent at low air pressures. A lack of surfactant causes the small airways to collapse and prevents air from entering the more distal alveoli. Alveolar air is then resorbed and the alveoli collapse. Air is redirected to small airways that have either some surfactant or a larger radius of curvature. The collapse of a large number of small airways causes the diffuse microatelectasis of the respiratory distress syndrome and the ground-glass appearance on radiography.

The Laplace law was applied in the past to the individual alveolus, erroneously assuming independent alveoli of spherical shape and constant curvature. Alveoli are, instead, interdependent, with flat polygonal surfaces. Radial traction from neighboring alveoli and the lung matrix resists alveolar collapse. The two-bubble model of Laplace's law applied to independent spherical alveoli is no longer presented in current texts.

Boyle's law states that, given a constant temperature, the product of a gas's pressure and its volume is constant. Charles's law states that, given a constant pressure, the ratio of a gas's volume to its temperature is constant. These relationships are often combined with the laws of Gay-Lussac and Avogadro to give the familiar ideal gas law:

$$PV = nRT$$

where $P$ is the pressure in pascals, $V$ is the volume in cubic meters, $n$ is the number of moles of gas, $R$ is the ideal gas constant (8.315 J/mol/K), and $T$ is the temperature in Kelvins. The ideal gas law allows calculations of gas exchange and ventilation, including the basic observation that delivering more gas to a lung (increasing $n$) will cause an increase in $P$ or $V$ or both.

Dalton's law states that the total pressure of a mixture of gases is the sum of each gas's partial pressure. This law is used in the alveolar gas equation when the partial pressure of water vapor at body temperature (47 mm Hg) is subtracted from the barometric pressure.

Poiseuille's law relates laminar flow in a tube to several factors. It is often reduced to the concept that the flow varies directly with the fourth power of the radius. This is useful to keep in mind when considering a change to a larger endotracheal tube. A change in inner diameter, from 2.5 mm to 3.0 mm, under the theoretical conditions of an ideal Newtonian gas and laminar flow, allows a doubling of gas exchange for the same pressure. In the cardiovascular system, it is more efficient to regulate blood flow by varying the diameter of a blood vessel than by varying blood pressure. Vasodilation by 50% will increase the blood flow by a factor of 5. A decrease in vessel diameter by 30% will reduce blood flow to one-quarter of its previous rate.

References:


**American Board of Pediatrics Content Specification(s):**

Understand the basic gas laws and how they apply to the clinical setting

Understand the pathophysiology of RDS

Recognize the radiographic features of RDS
An infant was born at 27 weeks' gestation and is now 5 days old. She has a clinically significant patent ductus arteriosus. The infant's resident calls you to report that no urine has been detected since indomethacin treatment was started 12 hours ago. You review the reasons for oliguria and the pathophysiology involving the renin-angiotensin system in preterm infants with the resident.

Of the following, the peptide MOST active in the lung is:

1. angiotensin I
2. angiotensin II
3. angiotensin-converting enzyme
4. angiotensinogen
5. renin

You selected 4, the correct answer is 3.

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A primary function of the renin-angiotensin system is maintenance of blood pressure and fluid volumes (Figures 1 and 2).

Figure 1: Renin-angiotensin system
When stimulated by a drop in blood pressure, the renin-angiotensin system becomes fully active in about 20 minutes. This system also responds to small changes in blood volume, and effects changes in water and sodium retention to maintain homeostasis. The main elements of the system are peptides acting in various body tissues. The main site of action of angiotensin-converting enzyme is the lung.

Renin is a proteolytic glycoprotein made of 340 amino acid residues. It is made and stored in the juxtaglomerular apparatus of the kidney. The stimuli for its release are decreased perfusion pressure in the afferent arterioles, decreased sodium reabsorption through the macula densa, or
beta-adrenergic stimulation by the sympathetic nervous system. Angiotensin II inhibits renin secretion. The half-life of renin in the circulation is 15 minutes.

Angiotensinogen, or renin substrate, is an α2-globulin made mainly in the liver. It is a glycoprotein with a molecular weight of 55 to 60 kD, containing 452 amino acid residues. It is split in the circulation by renin to form angiotensin I. Oral contraceptives with estrogen are thought to induce hypertension by increasing serum concentrations of angiotensinogen.

Angiotensin I is a decapeptide made from angiotensinogen in the circulation. It has only a mild vasoconstrictive effect. It serves mainly as a precursor for angiotensin II.

Angiotensin-converting enzyme is a glycoprotein with 1,277 amino acid residues and a molecular weight of 170 kD. It rapidly converts angiotensin I to the vasoconstrictor angiotensin II, and helps in the breakdown of the vasodilator bradykinin. It is made by endothelial cells of the vascular system, and is concentrated in the endothelial cells of the lungs.

Angiotensin II is an octapeptide made from angiotensin I by cleavage with angiotensin-converting enzyme. It is a strong vasoconstrictor, 40 times more potent than norepinephrine and 100 times more potent than angiotensin I. It acts within seconds after an acute dose, but is degraded within minutes. It acts on the arterioles to cause an increase in total peripheral resistance, and on the veins to augment venous return to the heart. It increases norepinephrine release from sympathetic nerves. In the kidneys, it stimulates the proximal tubule to reabsorb sodium. It causes the adrenal gland to make more aldosterone, which also increases salt and water retention.

The oliguria caused by indomethacin likely has two explanations. The first involves vasopressin. In the kidney of the premature neonate, prostaglandin E inhibits fluid retention caused by vasopressin and renin-angiotensin peptides. Indomethacin blocks the production of prostaglandin E, thereby allowing vasopressin and renin-angiotensin peptides to effect fluid retention and oliguria. Before the renin-angiotensin system can downregulate, the potent action of vasopressin combines with the normal action of the renin-angiotensin system to conserve water and cause oliguria.

A second explanation for the neonatal oliguria with indomethacin is based on the observation that indomethacin redistributes renal blood flow away from the mature nephrons of the inner cortex, toward the immature nephrons of the outer cortex. These nephrons have only a limited capacity to excrete sodium and water.

Oliguria associated with indomethacin use is not changed by the concurrent use of dopamine or furosemide, but may be reversed in experimental animal models with the use of a vasopressin inhibitor.

The short answer to the resident in the vignette is that indomethacin disturbs the balance in the kidneys between prostaglandins and the renin-angiotensin system, and between prostaglandins and vasopressin.

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References:


**American Board of Pediatrics Content Specification(s):**

Understand the pathway and control of angiotensin peptide production

Know the actions of the components of the renin-angiotensin system
You are meeting with the family of a term male infant who presented with abdominal distention associated with ileal atresia, for which an ileostomy was done. The colon was small. Although he had no pulmonary difficulties, cystic fibrosis was suspected based on the clinical presentation and confirmed with sweat chloride and genetic studies. After you present the need for referral to the cystic fibrosis clinic for ongoing nutritional support using pancreatic enzymes and for careful respiratory management, the family inquires about the future for patients having cystic fibrosis.

Of the following, the prognostic statement MOST consistent with the diagnosis of cystic fibrosis is that:

1. azoospermia will result in infertility
2. endocrine pancreatic function will remain normal
3. expected median survival is 25 years
4. osteopenia affects most adult patients
5. pancreatic enzyme supplements will prevent malnutrition

You selected 4, the correct answer is 1.

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive condition affecting the white population. Four percent of whites carry one of the over 800 mutations of the CF gene on chromosome 7. The incidence of CF (per live births) varies in different ethnic groups: 1 in 2,500 in whites, 1 in 17,000 in blacks, 1 in 9,200 in Hispanics, and 1 in 90,000 in Asians.

The genetic abnormality causing CF affects the function of the cystic fibrosis transmembrane conductance regulator (CFTR). Residing on the apical membrane of epithelial linings of the airways, biliary tree, intestines, pancreatic ducts, vas deferens, and sweat ducts, CFTR enables the transport of chloride at these sites and downregulates the resorption of sodium from secreted fluids. Individuals lacking CFTR function have insufficient fluid secretion combined with sodium/fluid resorption, resulting in hyperviscous secretions that may contain protein precipitates as well. Cells lacking CFTR fail to produce normal amounts of nitric oxide synthetase-2; the resultant reduction in nitric oxide contributes to increased sodium resorption, exaggerated inflammatory responses, and decreased bacterial killing. Other properties affected by CFTR abnormality include increased binding sites for Pseudomonas and upregulated proinflammatory pathways.

Diagnostic tests focus on the CFTR gene or its dysfunction: sweat chloride concentration exceeding 60 mEq/L (60 mmol/L); presence of two known CF mutations of the CFTR gene; or abnormal bioelectric testing of CFTR function in nasal epithelium. Currently, in most states,
newborn screening is indirect, in that it involves measurement of immunoreactive trypsinogen in blood (elevated in CF). Although most infants having CF will have positive test results, 80% of these results are false positive, requiring confirmation of the diagnosis with sweat testing or genetic testing. In the neonatal period, sweat testing has technical difficulties because of the low volume of sweat. Adequate sweat samples for testing usually are available after 1 month of age. Commercial genetic testing can identify almost all of the CF alleles, but some families with CF have unique (or private) mutations that are not detected with current tests. Delayed diagnosis will become less frequent as newborn screening becomes more effective and universal, making genetic counseling for CF a regular part of neonatal practice.

Of patients who have CF, 15% present with symptoms in the neonatal period, the most common manifestation being meconium ileus. Ninety percent of patients with meconium ileus have CF. Patients with either jejunal or ileal atresia have a 15% to 30% risk of CF, leading to the diagnosis of the infant in this vignette. An occasional patient will present with prolonged jaundice, the exact mechanism for which is unknown.

Although most individuals with CF are diagnosed by age 3 years, the initial presentation of CF can be subtle so that 1 in 20 cases is not diagnosed before age 16 years. Three elements define the CF phenotype, any one of which should lead to evaluation for CF: chronic sinopulmonary disease, gastrointestinal disease and/or malnutrition, and obstruction of the vas deferens (males).

The strongest determinant of survival and quality of life is pulmonary health. At birth, the lungs are histologically normal. Abnormality of the CFTR protein results in defective sodium and water balance resulting in shallow surface liquid layers, more viscous secretions, and in the lung, decreased ability to clear infected secretions. The endobronchial chronic infection and inflammatory changes result in bronchial damage with relative alveolar sparing. Bronchial mucous plugging, combined with infection and inflammation, ultimately results in bronchiectasis, initially involving the upper lobes and progressing to all the lobes of the lungs. Current long-term strategies include airway clearance using mechanical techniques, mucolysis (dornase alpha and hypertonic saline), inhaled antibiotics, antiinflammatory agents, and systemic antibiotics for exacerbations. Lung function is monitored regularly using forced expiratory volume, and 1% to 4% loss of lung capacity per year can be expected, even with treatment. Lung transplantation is reserved for the most severely affected patients and is performed on about 1.5% of the adult population with CF each year. The early and aggressive pulmonary treatment regimen in association with nutritional management has increased median survival to 36.9 years (2006 data) with 43% of all patients with CF now being older than 18 years of age.

Among infants with intact intestinal tracts, pancreatic exocrine insufficiency will be present in 90% of individuals. CF often presents as failure to thrive in an infant with good appetite and frequent foul-smelling stools. Treatment with pancreatic enzymes (amylase, lipase, and protease) lessens the impact of chronic malabsorption and should be begun early, but most patients will have chronic fat malabsorption. Because the acid-neutralizing effect of pancreatic secretions is diminished, use of acid inhibitors may augment the effect of orally administered pancreatic enzymes. Strategies such as high-caloric and high-sodium meals, supplementation with fat-soluble vitamins, and night-time tube feedings may be used. Nevertheless, patients with CF generally are somewhat undernourished with body mass indices lower than expected.

Vitamin D deficiency and decreased bone mineral content are common, affecting two-thirds of adults with CF. Osteoporosis results from combined effects of vitamin D malabsorption, inflammatory cytokines, low testosterone concentration, general malnutrition, and direct effect of the CFTR mutation on bone development. Deficiencies of vitamin K and vitamin E can occur. If vitamin E is necessary for shortened red blood cell survival or for peripheral neuropathy, the water-soluble form is needed.

In adults, distal intestinal obstruction syndrome can result from accumulation of solid stool at the ileocecal junction, where it normally should be liquid. Especially of concern among patients who are malnourished, not taking sufficient pancreatic enzyme supplementation, swallowing large volumes of mucous, and/or taking narcotics, treatment involves rehydration of the stool with osmotic laxatives or enemas. Adult patients with CF also present increased risk for cirrhosis, cholelithiasis, and nephrolithiasis, all suspected to be sequelae of CFTR dysfunction.
Adherent stools can create a lead point for intussusception, and poor tissue quality in the perirectal area can lead to rectal prolapse.

Congenital bilateral absence of the vas deferens (CBAVD) affects 99% of males with CF, resulting in obstructive aspermia. Eighty percent of CBAVD is associated with mutations of the CFTR gene. Although the vas is not patent, spermatogenesis is normal, and men with CF have fathered children through microepididymal sperm aspiration and in vitro fertilization. Fertility in females with CF is unaffected. Because CF is autosomal recessive, offspring of individuals with CF are usually not affected. Genetic testing of both parents can assess the risk for individual couples.

In addition to the pancreatic exocrine dysfunction, by adulthood, 20% to 30% of patients with CF have pancreatic endocrine dysfunction as the islets of Langerhans become strangulated by ongoing pancreatic fibrosis, resulting in CF-related diabetes. In this condition, release of insufficient amounts of insulin results in postprandial hyperglycemia, which may be precipitated by stresses such as pregnancy, treatment with corticosteroids, or pulmonary exacerbations. Because both insulin and glucagon are suppressed, diabetic ketoacidosis is rare. Management with short-acting insulin rather than with caloric restriction is needed to avoid worsening malnutrition. Recognition of and treatment for CF-related diabetes is important because of the association of poor diabetic control with neutrophil dysfunction, malnutrition, and risk for mortality.

Do you want to add anything to your Learning Plan?
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References:

Boyle MP. Adult cystic fibrosis. JAMA. 2007;298:1787-1793


American Board of Pediatrics Content Specification(s):

Know the long-term outcome and survival of infants with various congenital abnormalities

Understand the clinical manifestations and pathophysiology of cystic fibrosis in the newborn infant

Understand the diagnosis of cystic fibrosis in newborn infants

Understand the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis

Know the recurrence risks of various single-gene disorders
A 4.5-kg full-term male infant, who is delivered by emergency cesarean section, requires oxygen supplementation. You are reviewing the mechanisms of oxygen transport and delivery with the housestaff.

Of the following, the MOST accurate statement regarding oxygen kinetics in the newborn infant is that:

1. anaerobic metabolism begins when intramitochondrial O₂ is less than 40 mm Hg
2. oxygen consumption for normal neonates is approximately 6 mL/kg per minute
3. oxygen extraction ratio in normal newborns is approximately 40%
4. PaO₂ is the most important measurement to assess oxygenation in ill newborns
5. there is a linear relationship between O₂ delivery and consumption

You selected 5, the correct answer is 2.

Oxygen (O₂) consumption in normal neonates is approximately 6 mL/kg per minute. Understanding oxygen dynamics requires review of the movement of oxygen from the ambient or inhaled environment to the intracellular environment.

Gas exchange in the human body can be divided into two types: pulmonary and tissue respiration. Pulmonary respiration refers to the gas exchange between blood and inspired gas, while tissue respiration refers to the exchange of O₂ and carbon dioxide (CO₂) at the cellular level. O₂ passes from the atmosphere to the cells along a continuous diffusion concentration gradient (Figure 1).

Figure 1: Oxygen Gradient from the Inspired Air to the Cells
Oxygen makes up 21% of ambient air, which at sea level represents a partial pressure of 158 mm Hg. As the air is delivered to the distal airways and alveoli, PO$_2$ decreases by dilution with CO$_2$ and water vapor, and by uptake into the blood. Under ideal conditions, when ventilation and perfusion are well matched, the alveolar PO$_2$ will be approximately 100 mm Hg. This can be derived from the following alveolar gas equation:

$$PaO_2 = (\text{Barometric pressure} - \text{partial pressure of water vapor}) \times FIO_2 - PaCO_2/R$$

Where

- $PaO_2$ is the partial pressure of O$_2$ in the alveolar gas
- $PaCO_2$ is the partial pressure of CO$_2$ in the arterial blood as an estimate of alveolar gas
- $R$ is the respiratory quotient

The partial pressure of CO$_2$ in the alveoli is nearly identical to the amount of CO$_2$ physically dissolved in the arterial blood, or PaCO$_2$. The respiratory quotient is the ratio of CO$_2$ excretion to O$_2$ uptake. It ranges from 0.8 to 1.0 depending on the diet. Thus, in normal infants, the PaO$_2$ is 100 to 110 mm Hg. Under normal conditions, there is complete equilibration of alveolar gas and capillary blood. In some diseases, the diffusion barrier for gas transport may be increased, and the alveolar-end-capillary PO$_2$ gradient may be increased. The PO$_2$ in arterial blood is further reduced by venous admixture (shunt) and the addition of mixed venous blood from the pulmonary artery, which has a PO$_2$ of approximately 40 mm Hg. A combination of a small diffusion barrier, ventilation-perfusion mismatches, and the shunt fraction produces the alveolar-to-arterial oxygen gradient, which is normally 10 to 12 mm Hg when air is breathed and 30 to 50 mm Hg when 100% oxygen is breathed.

Oxygen is delivered to the tissue capillary beds by the circulation and again follows a gradient out of the blood, through the extracellular fluid, and into cells. The final gradient drives O$_2$ from the
extracellular fluid (PO₂ = 30 mm Hg) to the cytoplasm of the individual cell (PO₂ = 6-10 mm Hg). Although the PO₂ at the site of cellular oxygen utilization, or the mitochondria, is not known, oxidative phosphorylation can continue at a PO₂ of only a few millimeters of mercury. When the mitochondrial PO₂ falls below about 1 mm Hg, aerobic metabolism stops and the less efficient anaerobic pathway of glycolysis becomes responsible for the production of cellular energy.

In the blood, O₂ is carried primarily in chemical combination with hemoglobin and is to a small extent dissolved in solution. Thus, oxygen content (CaO₂) of blood can be expressed as follows:

\[ \text{CaO₂} = (\text{HbO₂}) + (\text{Dissolved O₂}) \]

Where HbO₂ is O₂ bound to hemoglobin, and Dissolved O₂ is the O₂ in solution.

The amount of O₂ carried in the blood by hemoglobin depends on the hemoglobin concentration, percentage of hemoglobin saturation, and O₂ capacity of hemoglobin. Mathematically, this is expressed as follows:

\[ \text{HbO₂} = (\text{g % Hb}) \times (\text{O₂ capacity}) \times (\% \text{ saturation}) \]

Hemoglobin O₂-carrying capacity is a constant that represents the maximum amount of O₂ that can be carried by a gram of hemoglobin. This value is 1.34 mL/g of hemoglobin.

The relationship between arterial oxygen tension (PO₂) and amount of O₂ combined with hemoglobin, or hemoglobin saturation, is sigmoidal over the physiologic range (Figure 2).

Hemoglobin is almost fully saturated at PO₂ of 80 to 100 mm Hg. Hemoglobin-bound O₂ accounts for the majority of the O₂ content in blood (Figure 3).
Only a small amount of O₂ is dissolved in the plasma (Figure 3). This amount is directly proportional to PO₂ from 0 to 600 mm Hg. At 38°C, 0.003 mL of O₂ is dissolved in 100 mL of plasma per mm Hg of O₂.

\[ \text{Dissolved O}_2 = (0.003 \times \text{PO}_2) \text{ mL/100 mL of plasma} \]

Assuming that a normal full-term newborn infant has a hemoglobin concentration of 15 g in 100 mL of blood, and that arterial blood is normally 100% saturated, the oxygen-carrying capacity of the blood (CaO₂) is:

\[ \text{CaO}_2 = (\text{HbO}_2) + (\text{Dissolved O}_2) \]

\[ = (\text{g % Hb}) \times (\text{O}_2 \text{ capacity}) \times (\% \text{ saturation}) + \text{Dissolved O}_2 \]

\[ = 20.10 + 0.3 \]

\[ = 20.4 \text{ mL per 100 mL arterial blood} \]

The amount of O₂ delivered to the tissues (DO₂) is dependent on the CaO₂ and cardiac output (CO). Assuming that the normal newborn CO is approximately 120 mL/kg per minute, the amount of O₂ that can be delivered to the systemic circulation is calculated as follows:

\[ \text{O}_2 \text{ delivered} = (\text{CO}) \times (\text{CaO}_2) \]

\[ = (120 \text{ mL/kg/min}) \times (0.204 \text{ mL O}_2/\text{mL blood}) \]

\[ = 24.48 \text{ mL O}_2/\text{kg/min} \]

The O₂ content is rarely measured directly for clinical applications, and it is standard practice to describe blood oxygenation in terms of PaO₂ or hemoglobin saturation. However, O₂ content is the more important measurement in the physiologic treatment of critically ill patients.

Oxygen consumption can be calculated as the product of the arteriovenous oxygen content difference multiplied by the CO (the Fick equation):

\[ \text{Oxygen consumption (VO}_2) = \text{Arterial O}_2 \text{ delivery} – \text{Venous O}_2 \text{ delivery} \]

\[ = \text{CO (CaO}_2 – \text{CvO}_2) \]

where CvO₂ is the content of O₂ in mixed venous blood.

Under normal circumstances, a neonate’s O₂ consumption is approximately 6 mL/kg per minute and the body extracts O₂ at a rate of 6 mL/kg per minute from the approximately 24 mL/kg per minute that is delivered to the systemic circulation. Therefore, the normal DO₂ is four to five times the V₉O₂ regardless of patient size (Figure 4) and 20% to 25% of the O₂ has been removed by the time it...
returns to the heart.

Figure 4

The mixed venous blood thus is 75% to 80% saturated. In general, a measured mixed venous saturation of 70% to 75% represents adequate tissue O₂ delivery. In patients in whom mixed venous saturation can be directly monitored (eg, patients receiving extracorporeal membrane oxygenation), the goal is to keep the mixed venous saturation in the normal physiologic range of 70% to 75%. Mixed venous blood hemoglobin saturation reflects the oxygen extraction ratio, and therefore it is the most important indicator for treating critically ill patients. If the arterial blood is fully saturated, the venous saturation decreases in proportion to the amount of O₂ extracted from the blood. Thus, if the O₂ extraction ratio is 20%, the venous saturation will be 80%; if the oxygen extraction ratio is 33%, the venous saturation will be 67%.

The normal relationship between DO₂ and V̇O₂ is biphasic (Figure 4). Above a critical threshold (point B in Figure 4), V̇O₂ is independent of DO₂. Below this threshold value, V̇O₂ decreases in a linear fashion with a decrease in DO₂. The critical threshold for DO₂ has been identified to be 3 to 5 mL/kg per minute or a ratio of DO₂ to V̇O₂ less than 2:1. However, the relationship of DO₂ to V̇O₂ may change during the course of a critical illness.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


Simon BA, Moody EJ, Johns RA. Therapeutic gases: oxygen, carbon dioxide, nitric oxide, and helium. 10th

**American Board of Pediatrics Content Specification(s):**

Know the causes of arterial hypoxemia in a patient with a structurally normal heart and how to differentiate among them using measurements of arterial blood gas tensions

Understand the basic gas laws and how they apply to the clinical setting

Understand the various factors affecting oxygen uptake, transport, and delivery, including the blood and circulation
A 4.5-kg term male newborn was delivered by emergency cesarean for a nonreassuring fetal heart rate pattern. Apnea, hypotonia, and acrocyanosis were present at birth; the heart rate was greater than 100 beats per minute. Apgar scores were 6 and 7 at 1 and 5 minutes, respectively. Manual ventilation was provided and the infant was placed on positive pressure ventilation with a fraction of inspired oxygen (FiO₂) of 0.6, peak inspiratory pressure (PIP) of 18 cm H₂O, positive end-expiratory pressure of 4 cm H₂O, and ventilator rate of 30 breaths per minute. His blood pressure was 75/54 mm Hg and oxygen saturation 100%. Initial studies were as follows.

<table>
<thead>
<tr>
<th>Laboratory Findings</th>
<th>Patient Results (SI Values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total WBC count, ×10⁹/µL (×10⁹/L)</td>
<td>8.2 (8.2)</td>
</tr>
<tr>
<td>WBC differential</td>
<td></td>
</tr>
<tr>
<td>Segmented cells, %</td>
<td>65</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>30</td>
</tr>
<tr>
<td>Platelet count, ×10⁹/µL (×10⁹/L)</td>
<td>150 (150)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL (g/L)</td>
<td>10 g/dL (100)</td>
</tr>
</tbody>
</table>

Chest radiograph shows clear lung fields, lung expansion to 8 ribs, normal cardiac silhouette. Echocardiogram shows normal cardiac anatomy, left to right shunting across the foramen ovale and ductus arteriosus. Arterial blood gases were as follows: pH 7.30, PaCO₂ 44 mm Hg, PaO₂ 100 mm Hg, bicarbonate 21 mEq/dL (22 mmol/L).

Of the following, the intervention MOST likely to increase oxygen delivery in this infant is:

1. dopamine infusion
2. increase in FiO₂
3. increase in PIP
4. inhaled nitric oxide
5. RBC transfusion

You selected 3, the correct answer is 3.

---

The amount of oxygen (O₂) that can be delivered to the tissues (DO₂) depends on two major factors: cardiac output (CO) and the O₂ content of the blood (CaO₂). This can be expressed as follows:

\[ \text{O}_2 \text{ delivery (DO}_2\text{) = (CO) × (CaO}_2\text{)} \]

The O₂ content of arterial blood (CaO₂) depends on the amounts of O₂ bound to hemoglobin (HbO₂) and dissolved in the plasma (dissolved O₂). Hemoglobin-bound O₂ is quantitatively the...
most important contributor to CaO₂ because the amount of O₂ dissolved in blood is very small at normal PaO₂. The CaO₂ of blood is expressed as follows:

\[ \text{CaO}_2 = (\text{HbO}_2) + \text{(dissolved O}_2) \]

The amount of O₂ carried in the blood by hemoglobin depends on the concentration of hemoglobin (g % Hb), percentage of hemoglobin saturation (% saturation) and O₂ capacity of hemoglobin. Mathematically, this is expressed as follows:

\[ \text{HbO}_2 = (\text{g} \% \text{ Hb}) \times (\text{O}_2 \text{ capacity}) \times (\% \text{ saturation}) \]

O₂ capacity is a constant that represents the maximum amount of O₂ that can be carried by a gram of hemoglobin. This value is 1.34 mL/g of hemoglobin.

The relationship between arterial oxygen tension (PO₂) and amount of O₂ combined with hemoglobin, or hemoglobin saturation, is sigmoidal over the physiologic range (oxyhemoglobin dissociation curve). Hemoglobin is almost fully saturated at PO₂ of 80 to 100 mm Hg (Figure 1).

**Figure 1:** The relationship between arterial oxygen tension (PO₂) and hemoglobin saturation

\[
\begin{align*}
\text{Hemoglobin Saturation} &\quad 0 &\quad 10 &\quad 20 &\quad 30 &\quad 40 &\quad 50 &\quad 60 &\quad 70 &\quad 80 &\quad 90 &\quad 100 \\
\text{PO₂ (mm Hg)} &\quad 0 &\quad 20 &\quad 40 &\quad 60 &\quad 80 &\quad 100 &\quad 120 &\quad 140 &\quad 160 \\
\end{align*}
\]

A small amount of O₂ is dissolved in the plasma (Figure 2).

**Figure 2:** The O₂ content of arterial blood (CaO₂) depends on several factors, the most important being the O₂ bound to hemoglobin. In addition, some O₂ is carried in dissolved form in plasma.
This amount is directly proportional to PO\textsubscript{2} from 0 to 600 mm Hg. At 38°C, 0.003 mL of O\textsubscript{2} is dissolved in 100 mL of plasma per mm Hg of O\textsubscript{2}.

\[
\text{Dissolved O}_2 = (0.003 \times \text{PO}_2) \text{ mL/100 mL of plasma}
\]

Assuming that a normal term newborn infant has a hemoglobin concentration of 15 g/100 mL of blood, and that arterial blood is normally 100% saturated, the CaO\textsubscript{2} is:

\[
\text{CaO}_2 = (\text{HbO}_2) + (\text{Dissolved O}_2)
\]

\[
= [(\text{g \% Hb}) \times (\text{O}_2 \text{ capacity}) \times (\% \text{ saturation})] + \text{Dissolved O}_2
\]

\[
\text{CaO}_2 = (15) \times (1.34) \times (1.0) + (0.003 \times 100)
\]

\[
= 20.10 + 0.3
\]

\[
= 20.4 \text{ mL per 100 mL of arterial blood}
\]

Assuming that the normal newborn cardiac output is approximately 120 mL/kg per minute, the amount of O\textsubscript{2} that can be delivered by the systemic circulation is calculated as follows:

\[
\text{O}_2 \text{ delivered} = (\text{CO}) \times (\text{CaO}_2)
\]

\[
= (120 \text{ mL/kg per minute}) \times (0.204 \text{ mL O}_2/\text{mL blood})
\]

\[
= 24.48 \text{ mL O}_2/\text{kg per minute}
\]

The infant in this vignette has a lower than normal concentration of hemoglobin (10 g/dL [100 g/L]). An increase in hemoglobin concentration to 15 g/dL (150 g/L) after an RBC transfusion will increase the CaO\textsubscript{2} from 13.7 mL/100 mL of arterial blood to 20.4 mL/100 mL of arterial blood; the delivered O\textsubscript{2} will be 24.48 mL/kg per minute (Figure 3). Of note, the CaO\textsubscript{2} of blood with a hemoglobin concentration of 15 g/dL at a PO\textsubscript{2} of 40 mm Hg is higher than that of anemic blood at PO\textsubscript{2} of 100 mm Hg.
Figure 3: Effect of hemoglobin concentration and oxygen tension on oxygen content (CaO₂) of blood

The infant in the vignette is normotensive, and has normal perfusion. Cardiac activity appears normal on echocardiography. The normal neonatal heart functions at near capacity with stroke volume and heart rate maximized. Cardiac output (stroke volume × heart rate), therefore, is normally maximized. Administration of dopamine will increase systemic vascular resistance and, to a lesser degree, cardiac contractility but is unlikely to substantially increase cardiac output in this case.

The PaO₂ in the infant in the vignette is 100 mm Hg and oxygen saturation (Sao₂) is 100%. Increasing PaO₂ by increasing either FiO₂ or peak inspiratory pressure will not significantly affect the hemoglobin bound O₂ because the oxyhemoglobin dissociation curve is flat above a PaO₂ of 90 mm Hg.

Because O₂ is poorly soluble in blood, increasing the PaO₂ will not significantly increase the amount of dissolved O₂; therefore CaO₂ does not change appreciably. Even if the PaO₂ is increased to 400 mm Hg, only 0.9 mL of O₂/100 mL of blood is added to the CaO₂.

Inhaled nitric oxide functions to lower pulmonary vascular resistance when it is elevated, thereby increasing PaO₂ and SaO₂. Inhaled nitric oxide does not affect pulmonary vascular resistance when it is normal. Therefore, treatment with inhaled nitric oxide is unlikely to raise the PaO₂ and oxygen delivery in the infant in the vignette.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


American Board of Pediatrics Content Specification(s):

Know the causes of arterial hypoxemia in a patient with a structurally normal heart and how to differentiate among them using measurements of arterial blood gas tensions

Understand the basic gas laws and how they apply to the clinical setting

Understand the various factors affecting oxygen uptake, transport, and delivery, including the blood and circulation
A preterm infant is getting ready to be discharged home at 35 weeks’ postmenstrual age. As the infant falls asleep after a full feed by bottle, you notice that the infant is taking a few slow deep breaths, much like an adult sigh. You think about the control mechanisms that may be contributing to such a breathing pattern.

Of the following, the respiratory control mechanism MOST likely to contribute to the lung inflation of a neonatal sigh is the sensitivity of the:

1. chemoreceptors of the carotid bodies to hypoxemia
2. chemoreceptors of the ventral medulla to carbon dioxide
3. irritant receptors of the airways to stretch
4. phrenic nerve to distorted intercostal output
5. stretch receptors of the airways to stretch

You selected 3, the correct answer is 3.

Do you want to add anything to your Learning Plan?
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Several important pulmonary reflexes and control mechanisms are seen in the neonate. The reflex most likely to be involved in a neonatal sigh is the stimulation of the pulmonary irritant receptors, causing a deep inspiration (Head's paradoxical reflex). Hypoxemic stimulation of the carotid bodies causes an immediate tachypnea, as does carbon dioxide stimulation of the ventral medulla. Stimulating the stretch receptors of the airways causes apnea (Hering-Breuer reflex). A distorted output from the intercostal nerves inhibits the phrenic nerve and causes a shortened inspiratory time.

Head's paradoxical reflex is seen when a rapid inflation of the lungs causes a deep inspiration or gasp. It is mediated by the irritant receptors in the mucosa of the major airways. These receptors are also receptive to lung inflation. The reflex is seen most often on the first day, and may act as a way to establish and maintain a functional residual capacity. Later in the neonatal period, it facilitates the large lung expansion of sighs, but the exact trigger for neonatal sighs is not well known. In some cases, neonatal sighing may be followed by apnea. Head's paradoxical reflex is rarely seen in adults.

The chemoreceptors of the carotid bodies and, to some extent, the aortic bodies, respond to decreases in blood oxygen concentration by causing brainstem stimulation, which in turn causes an immediate increase in respiratory rate and tidal volume. This process is mediated by potassium channels and linked to calcium influx.

The response to hypoxemia is biphasic in both adults and infants, initially showing an increase in minute ventilation and then a decrease in minute ventilation after 1 to 2 minutes of hypoxemia in the premature infant, and after 5 minutes in the adult. The adult minute ventilation in the second phase of the response remains above the baseline rate. However, the second phase response is more pronounced in premature infants, resulting in minute ventilation that is below the baseline. The mechanism of this latter decrease in minute ventilation is thought to involve central respiratory depression secondary to hypoxemia.
The response to hyperoxia is mediated by the carotid bodies, and is also biphasic: an immediate decrease in respiratory rate and tidal volume is followed by a later increase. The later increase may be caused by cerebral vasoconstriction leading to an increase in the hydrogen ion concentration, stimulating the ventral medullary respiratory center.

The chemoreceptors of the ventral medulla respond to increases in blood carbon dioxide or hydrogen ion concentrations by triggering a faster respiratory rate and deeper breaths. A change in the hydrogen ion concentration is a stronger stimulus than is a change in the carbon dioxide concentration. The increase in minute ventilation, resulting from an increase in carbon dioxide or hydrogen ion concentration, is blunted by prematurity, hypoxia, or sedation. Premature infants with apnea have an even more blunted response than premature infants without apnea.

The intercostal-phrenic inhibitory reflex is seen when distortion of the intercostal muscles, worsened by the compliant chest wall of the premature infant, causes an inhibition of the output to the phrenic nerve. The result is a shorter inspiratory time. Nasal continuous positive airway pressure or prone positioning can reduce intercostal distortion, increasing the inspiratory time and slowing the respiratory rate.

The inflation reflex of Hering-Breuer occurs when a small but sustained increase in inspiratory tidal volume results in a short period of apnea. The reflex is mediated by the stretch receptors in the smooth muscles of the major airways, and also to some degree by the irritant receptors. This reflex is time-dependent: a longer inspiratory time results in a longer period of respiratory inhibition before the next breath is taken. Endotracheal mechanical ventilation or nasal continuous positive airway pressure can trigger this reflex, causing slower spontaneous respiratory rates. The Hering-Breuer inflation reflex is rarely seen in adults.

Interestingly, there is a deflation reflex of Hering-Breuer. In response to decreased lung volumes, atelectasis, or airway collapse, the neonatal respiratory rate increases. The effect is achieved by shortening the expiratory time, which then helps to maintain or enhance functional residual capacity.

References:


American Board of Pediatrics Content Specification(s):

Understand the effects of pulmonary reflexes and oxygen, carbon dioxide, and hydrogen ion concentration on control of neonatal breathing

Know factors that determine residual lung volume, functional residual capacity, and tidal volume, and how they change with various pulmonary disorders
A pregnant woman with diabetes is planning to deliver her neonate with macrosomia through a cesarean section at 38 weeks' gestation. The parents are reviewing the possible medical issues that may arise for the newborn after birth. After you discuss treatment options, including the use of surfactant, you explain to the house staff the physical chemistry of surfactant.

Of the following, a decrease in surface tension at the air-liquid interface on the alveolar surface induced by surfactant is MOST likely the result of:

1. critical transition temperature below 37ºC
2. high concentration of sodium and chloride in water phase
3. high saturated-to-unsaturated phospholipid ratio
4. long chain lengths of fatty acyl groups
5. phospholipid displacement of water molecules

You selected 4, the correct answer is 4.

Do you want to add anything to your Learning Plan?
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Surface tension occurs because molecules on the surface of an air-liquid interface are attracted by molecules in the bulk phase of the liquid rather than air. The net effect is that surface molecules are drawn into the bulk phase of the liquid and the surface area is minimized. To overcome the forces on surface molecules requires energy. For example, at 37ºC, the energy to move water molecules to the surface and expand the surface area is 70 mJ/cm².

In the water layer lining alveolar saccules, molecules of water in the liquid phase attract water molecules that are present at the air-liquid interface (ie, surface tension). Surface tension resists expansion of alveolar saccules and must be overcome by tissue forces and respiratory work to maintain functional residual capacity and minute ventilation.

The surface tension of a fluid is modified by the presence of various molecules on its surface and within the liquid layer, physicochemical properties, and temperature. Dipalmitoylphosphatidylcholine (DPPC) is the predominant phospholipid responsible for reducing surface tension at the air-liquid interface of the lung. DPPC, an amphipathic molecule, has both hydrophilic phosphorylcholine head groups that extend into the liquid phase and hydrophobic fatty acyl groups that extend into the air. By physically displacing water molecules from the air-liquid surface, surface tension is reduced and the volume of gas in alveolar saccules is stabilized.

Surface tension in monolayers of DPPC continues to decrease with additional DPPC molecules until the equilibrium surface tension for phospholipid monolayers is achieved. At the equilibrium surface tension, additional phospholipids will not spontaneously adsorb to the monolayer and reduction in surface tension is optimized. Although the composition of the water film and temperature will affect the absolute value, the equilibrium surface tension for phospholipid monolayers is estimated to be about 23 milliNewtons per meter (mN/m).

The rate of DPPC monolayer formation is relatively slow at 37ºC and when DPPC is dry or only partially hydrated. By increasing the temperature to 41ºC, fully hydrating DPPC, or both, the phospholipids spread more rapidly to form monolayers. Like other biologic membranes, hydrated
DPPC molecules that are heated to a critical transition temperature of 41°C undergo a change from a relatively nonmobile state to a disordered, more fluid state. In a disordered and fluid state, DPPC molecules are absorbed and diffuse more quickly within the membrane to reduce surface tension.

Sodium and chloride attract water molecules. The presence of sodium and chloride within the film lining alveolar saccules tends to increase surface tension.

Phospholipids such as DPPC, which contain fatty acyl groups at the sn-2 position of the glycerol moiety that are saturated (content of hydrogen ions is maximized and carbons are only connected by single bonds), are more easily packed together than unsaturated phospholipids but are slower to form monolayers at physiologic temperatures. The double bonds of unsaturated phospholipids are kinked so they consume more space within the air-fluid interface of alveolar saccules, introduce fluidity, and reduce the critical transition temperature of the monolayer. Surface tension is reduced at physiologic temperatures when unsaturated phospholipids are predominant. Similarly, shortening the chain length of saturated fatty acids reduces the critical transition temperature. Monolayers with phospholipids containing unsaturated or short fatty acyl side groups introduce fluidity and reduce surface tension at 37°C.

Adsorption of DPPC at 37°C to form monolayers can be accelerated by unsaturated phosphatidylcholine, unsaturated phosphatidylglycerol, unsaturated phosphatidyethanolamine, unsaturated phosphatidylinositol, and cholesterol contained in pulmonary surfactant. Other lipids such as palmitic acid, hexadecanol, and dipalmitoylglycerol also increase adsorption of DPPC. However, the influence of unsaturated phospholipids and other lipids on DPPC adsorption, membrane fluidity, and surface tension in the film lining the human lung is small.

Surfactant-associated proteins, especially surfactant-protein B (SPB) and surfactant-protein C (SPC), have a major influence on DPPC adsorption into the phospholipid monolayer at the air-liquid interface. Such proteins are also important for movement of lipids within the air-liquid surface film of the lung. In the absence of surfactant-associated proteins, lethal (SPB) or chronic (SPC) respiratory insufficiency occurs in humans and animal models. Surfactant-associated proteins promote adsorption and spreading of surfactant lipids to directly lower surface tension, modify the physical state of the film to facilitate a surface tension as low as 0 mN/m, and accelerate transfer of lipids from tubular myelin and surface-associated phospholipid reservoirs (compression reservoirs or pleats of phospholipids).

Pulmonary surfactant, highly enriched with DPPC and surfactant-associated proteins, reduces surface tension and acts as a surface “splint” during exhalation (Figure).

Figure: Lateral compressive forces during exhalation align dipalmitoylphosphatidylcholine (DPPC) and force water molecules from the air-liquid interface. Surface tension is reduced and the DPPC monolayer acts as a splint so that alveolar saccules do not collapse.
Films of DPPC are stable at 37°C and easily packed together to exclude water molecules from the surface layer. During exhalation, dynamic lateral compressive forces on alveolar saccules peak and condense islands of DPPC molecules at the air-liquid interface. As alveolar saccules are squeezed, the following changes occur in the surface monolayer to stabilize alveolar saccules:

- DPPC is packed tightly and lowers surface tension to about 0 mN/m (vs 23 mN/m, the equilibrium surface tension of DPPC monolayers).
- DPPC membranes transition from a liquid state to a compressed, solid gel state that physically resists collapse.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:


American Board of Pediatrics Content Specification(s):

Determine the effects of surface tension on alveolar and airway stability and lung mechanics (LaPlace law)

Understand the management of RDS, including surfactant replacement
A 31-week-gestation, 1,250-g male infant is delivered by cesarean section because of fetal heart rate decelerations. The pregnancy was complicated by diet-controlled gestational diabetes. Prenatal ultrasonography at 18 weeks demonstrated normal fetal anatomy. The infant was vigorous at birth; Apgar scores were 8 and 8 at 1 and 5 minutes, respectively. Six minutes after delivery, he developed grunting, subcostal retractions, and cyanosis. A pulse oximeter placed on the right foot demonstrated an oxygen saturation of 76% in room air, which increased to 95% in 35% oxygen. Nasal continuous positive airway pressure is applied at 8 cm H₂O. Figure 1 depicts a static pressure-volume loop.

![Figure 1: Static pressure-volume loop](image)

Of the following, the points on the pressure volume curve associated with the HIGHEST pulmonary vascular resistance are:

1. A and B
2. A and C
3. B and C
4. B and D
5. C and D

You selected 4, the correct answer is 2.
The infant in this vignette has clinical symptoms consistent with surfactant deficiency. Surfactant deficiency results in low lung volume (atelectasis) because of high surface tension and absence of the “splinting” effect of condensed dipalmitoylphosphatidylcholine at the air-liquid interface in terminal respiratory units. Without adequate concentration or function of surfactant, the infant may not be able to generate enough inspiratory pressure to inflate alveolar saccules. Hypoxemia results from intrapulmonary shunting across atelectatic alveolar saccules and right-to-left shunting across the foramen ovale or ductus arteriosus.

Continuous positive airway pressure (CPAP) improves oxygenation in surfactant deficiency by enhancing the release of surfactant, conserving the surfactant present on the alveolar surface, and providing end distending pressure during exhalation. These effects then aid lung expansion; increase lung volume, especially functional residual capacity (FRC); improve ventilation-perfusion matching; and decrease pulmonary vascular resistance (PVR). PVR is lowest at optimal FRC (30 mL/kg) and when lung volume and pressure change during inflation (Figure 1, B) and deflation (Figure 1, D). Changes in lung volume affect PVR by passive compression of pulmonary blood vessels and by hypoxic pulmonary vasoconstriction.

A low lung volume state is identified by A in the pressure-volume loop (Figure 1). Diffuse atelectasis results in low compliance, high resistance in collapsed small airways, and low FRC. Hypoxemia results primarily from mismatching of ventilation and perfusion as blood bypasses atelectatic air spaces (intrapulmonary shunting). Hypoxic vasoconstriction then elevates PVR, which also rises with atelectasis because extra-alveolar blood vessels become more tortuous and collapsed. Increased PVR may result in right-to-left shunting through the ductus arteriosus and foramen ovale and contribute to decreased oxygenation.

Lung inflation immediately after birth initially decreases PVR as FRC is established. As the lung inflates beyond FRC, intra-alveolar pressures rise, intra-alveolar vessels are compressed by the surrounding airways and elevated airway pressure, and PVR increases; this is depicted by letter C (Figure 1). Inadvertent overdistention of the lung with positive pressure also increases physiologic dead space, decreases tidal volume because compliance worsens, and may lead to a rise in partial pressure of carbon dioxide (PCO₂). Elevated PCO₂ also causes PVR to rise.

Overdistension of the lung with positive pressure (such as CPAP) may cause pulmonary parenchymal injury in addition to changes in PVR. Such complications include pneumothorax, pneumomediastinum, pneumopericardium, and pneumoperitoneum. Pulmonary air leaks occur because of overdistention of the more compliant units of the lungs.

When CPAP is applied to surfactant-deficient lungs, compliance improves and lung volume rises or falls with small changes in pressure during lung inflation and deflation (B and D in Figure 1). PVR likely rises only to a small degree above that found when the lung is at FRC (Figure 2).
Lung volumes greater than FRC may splint open some distal pulmonary vessels. However, when lung volume and airway pressure are excessive (C in Figure 1), PVR increases.

Continuous positive airway pressure has additional effects on neonatal ventilation other than increases in lung volume, compliance, and minute ventilation. CPAP produces a more regular breathing pattern in premature infants, which is thought to be mediated through chest wall stabilization and diminished thoracic distortion. Surfactant release appears to be enhanced by CPAP as well.

Continuous positive airway pressure increases lung volume and airway pressure, therefore pressure transmission into the thoracic cavity and secondary effects on circulation may cause negative consequences outside the lung. For example, excessive pressure transmitted to the cardiovascular system can result in elevations in central venous pressure and intracranial pressure; changes in intracranial pressure may lead to increased risk for intracranial hemorrhage. The renal effects of nasal CPAP depend on lung compliance; the more compliant the lungs the greater is the transmission of distending pressure to the intrathoracic structures. Increased intrathoracic pressure potentially impedes venous return and secondarily decreases cardiac output. Renal dysfunction during CPAP may result from such systemic hemodynamic alterations.

References:


American Board of Pediatrics Content Specification(s):
Understand the effects and risks of CPAP
Recognize the clinical and laboratory features of air leaks
Recognize the laboratory features of air leaks
Know how intrapleural pressure affects cardiovascular function
Understand the indications for and techniques of continuous positive airway pressure (CPAP)
June: Question 1

A 135-day-old ventilator-dependent male infant with chronic lung disease and posthemorrhagic hydrocephalus has a tracheostomy placed for ongoing respiratory management. On the second postoperative day, he becomes restless, his heart rate drops to 60 beats per minute and his oxygen saturation falls to 70%. Physical examination shows retractions, decreased breath sounds over both lung fields, and poor chest wall excursion. A capillary blood gas measurement has a pH of 7.09 and a Paco₂ of 94 mm Hg (15.7 kPa). His chest radiograph is shown (Figure).

Figure: Radiograph showing tracheostomy (courtesy of Robert Wells, MD).

Of the following, the MOST likely cause of the neonate's condition is a:

1. cannula dislodgement
2. cannula obstruction
3. pneumonia
4. pneumothorax
5. tracheal hemorrhage

You selected 2, the correct answer is 2.

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The rate of tracheostomy placement in neonates has steadily declined during the past two decades. Because of improved endotracheal tube design and improvements in neonatal care, tracheostomies among hospitalized neonates have declined from 2.7% in 1978 to 0.55% in 2001. The primary indication for tracheostomy in neonates has gradually shifted from upper airway obstruction to prolonged ventilatory support. In one recent series of neonates, indications for tracheostomy included:

- ventilator dependency (69% of cases)
- airway obstruction (24%)
In a large series of pediatric tracheostomies, prematurity was listed as an indication in 58% of patients.

Among children younger than 1 year of age who require a tracheostomy, 13% to 30% will have a tracheostomy-related complication. Mortality from the procedure is approximately 2% among infants younger than 1 year. The most common complications occurring during the week following cannula placement are:

- bleeding
- skin breakdown
- cellulitis
- pneumothorax or pneumomediastinum
- tracheostomy obstruction
- inadvertent decannulation

The neonate in this vignette has signs (retractions, cyanosis, decreased breath sounds, and poor chest excursion) consistent with airway obstruction. Cannula obstruction occurs in up to 72% of neonates who have undergone tracheostomy placement, and is the most common early postoperative complication. Cannula obstruction from secretions is also the most common cause of tracheostomy-related death. The higher rate of obstruction in newborns is likely related to the narrow inner diameter of the tracheostomy cannula and the fact that many neonates requiring tracheostomies have viscous bronchial secretions from their chronic lung disease. Adequate humidification and frequent suctioning during the first several days after surgery will help limit tracheostomy obstruction.

Up to 7% of premature or newborn infants undergoing tracheostomy experience an inadvertent cannula dislocation or decannulation. Inadvertent cannula dislocation or decannulation can happen at any time and often goes unnoticed. It is one of the most common causes of tracheostomy-related deaths. Following cannulation, the tracheostomy tract matures in 5 to 7 days. Until the tract is formed, attempting to blindly reinsert a decannulated tracheostomy tube can cause significant morbidity if the tube should enter the anterior mediastinum or perforate the posterior trachea. Ensuring that tracheal ties are secured in the operating room and using sedation liberally during the first postoperative week will help to prevent unplanned dislodgment. Tracheal traction sutures, placed at the time of surgery, will help ensure safe replacement of a dislodged tube by experienced caregivers during the first postoperative week. Additional tracheostomy tubes, one of the same size and the other a size smaller, should be stored at the bedside. Placing an endotracheal tube from above may be the safest option in the absence of a caregiver skilled in replacing a dislodged cannula during the immediate postoperative period. The radiograph of the neonate in the vignette shows the tracheostomy tube to be well positioned within the trachea (Figure).

Pneumonia, a frequent complication after the first postoperative week, is uncommon during the immediate postoperative period. The neonate in the vignette did not have symptoms consistent with pneumonia and the chest radiograph was not suggestive of pneumonia.

The most common postoperative complication of tracheostomy placement in pediatric patients is the development of interstitial air (emphysema, pneumothorax, pneumomediastinum). Pneumothorax occurs in up to 28% of neonates who undergo a tracheostomy. Pneumothorax and pneumomediastinum may occur after injury to the dome of the pleura during tracheostomy placement. Limiting dissection during placement can decrease the risk of an air leak. Radiographic findings of the infant in the vignette are not consistent with a pneumothorax.

Tracheal hemorrhage is the most common intraoperative complication, and occurs in up to 5% of neonates after a tracheostomy. Without evidence of bleeding at the site of the tracheostomy, hemorrhage is an unlikely cause of airway obstruction in the infant in the vignette.
References:


American Board of Pediatrics Content Specification(s):

Understand the clinical features of an infant with airway obstruction, such as vascular rings, choanal atresia, and tracheal abnormalities

Know the indications for, complications of, and surgical management of tracheostomies
A child is born at 28 weeks' gestation after a precipitous vaginal delivery. No prenatal steroids were given. He is brought to the nursery in moderate respiratory distress. He is placed on a warmer. In the adjacent bed, a 3-month-old child born at 25 weeks gestation is receiving nasal continuous positive airway pressure and 35% oxygen. As one of your residents prepares for endotracheal intubation and surfactant administration, you ask the other residents on your team to consider how the cardiovascular function of the two children is affected by their two lung diseases, respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD).

Of the following, severe RDS and severe BPD differ MOST in their effects on:

1. extra-alveolar vessel constriction
2. B-natriuretic protein expression
3. intrapulmonary shunting
4. pulmonary artery pressure
5. right ventricular dilation

You selected 3, the correct answer is 1.

Respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) share several effects on the heart and blood vessels. Both diseases are associated with increases in B-natriuretic protein expression, intrapulmonary shunting, pulmonary artery pressure, and right ventricular dilation. The diseases differ in how they affect extra-alveolar vessels: RDS causes increased constriction, while BPD results in dilation.

The blood vessels in the lung can be classified as alveolar, running in the alveolar septa, or as extra-alveolar, running in the perivascular cuffs and the interlobular septa. The alveolar vessels comprise the main pulmonary capillary bed and are susceptible to alveolar pressures. As the alveolar pressure increases, as with mechanical ventilation using a large distending pressure, the alveolar vessels are compressed, and the vascular resistance for these vessels increases (Figure).

**Figure: Expansion of blood vessels in the lungs (adapted from Hansen and Corbet [2005])**
The extra-alveolar vessels are stretched open as lung volume expands, and the vascular resistance for these vessels decreases. The total pulmonary vascular resistance is the sum of the alveolar and extra-alveolar resistances, and reaches a minimum when lung volumes are at the ideal functional residual capacity (FRC). Above the ideal FRC, total pulmonary vascular resistance increases because of the alveolar resistance. Below the ideal FRC, the total pulmonary resistance also increases, but now secondary to the extra-alveolar resistance.

In RDS, a lower than ideal FRC results in constriction of the extra-alveolar vessels. The increased pulmonary vascular resistance causes a high pulmonary artery pressure, and may prevent closure of the ductus arteriosus.

The alveolar vessels in BPD are abnormally small because of the thickened fibrotic walls of the alveoli constricting the vessels as fibrosis worsens. The overdistended air sacs constrict the alveolar vessels stretched taut on their surfaces (Figure). The dysplastic branching of the airways and the blood vessels is most chaotic at the alveolar level and causes abnormal flow and increased resistance. The slow cell division and growth in the lungs at the alveolar capillary level gives an abnormally small capillary bed and contributes to total pulmonary vascular resistance.

The extra-alveolar vessels in BPD are found to be larger than normal, in reaction to the increased alveolar capillary pressure and the increased metabolic demands of the extra smooth muscle that proliferates abnormally down the respiratory branches to the bronchiolar level. These larger vessels may form anastomoses with pulmonary veins, contributing to intrapulmonary shunting.

Secondary to increased pulmonary artery pressure, right ventricular dilation occurs in both RDS and BPD. The chronic dilation seen in BPD is followed by right ventricular hypertrophy, a process that may begin after only a few days of elevated pulmonary artery pressure. BPD is associated with left ventricular strain also, caused by the afterload of systemic hypertension and the need to pump against the high negative intrathoracic pressures generated by breathing. Catecholamines are not cleared well by the pulmonary vasculature in BPD, adding to the systemic hypertension.

B-natriuretic protein (BNP) is a 32-residue peptide produced by cardiomyocytes in response to excessive stretching of the ventricles. It is increased in BPD secondary to the strain placed on both ventricles by the elevated pulmonary artery pressure and systemic hypertension. BNP is increased in all newborns, and remains high in RDS because of the elevated pulmonary artery pressure. It also remains high when an open ductus arteriosus, a frequent concomitant of RDS, leads to excessive strain on the left ventricle. A related peptide fragment, NT-proBNP, has a longer half-life than BNP, and is being investigated as a marker of impending cardiac failure in the neonate.
Intrapulmonary shunting occurs in both RDS and BPD as blood traverses the capillaries of alveoli that are collapsed or ineffectually ventilated.

**References:**


**American Board of Pediatrics Content Specification(s):**

Understand how acute and chronic lung disease affects cardiovascular function

Understand the pathophysiology of RDS

Understand the pathogenesis and pathophysiology of bronchopulmonary dysplasia/chronic lung disease
A term newborn, delivered with the help of vacuum extraction, has cyanosis, a heart rate of less than 80 beats per minute, and ineffectual grunting respirations. The infant’s father, who is completing his PhD in molecular biology, expresses his amazement as his son’s cyanosis dissipates with the positive pressure ventilation and supplemental oxygen you provide. He is curious as to what cellular mediators and receptors are responsible for resolution of his son’s cyanosis.

Of the following, the cell mediator or receptor that MOST likely contributes to pulmonary vascular vasodilation at birth is:

1. angiotensin II
2. leukotrienes
3. potassium channels
4. type A endothelial receptors
5. vascular endothelial growth factor

You selected 3, the correct answer is 3.

Pulmonary arterial blood flow increases eight to 10-fold and pulmonary vascular resistance (PVR) drops 50% within 24 hours after birth. Mechanical lung inflation, increased oxygen tension, shear stresses, and vasoactive factors all contribute to vasodilation of the pulmonary circulation. A number of cell mediators and cell receptors are involved in the dramatic changes seen in the pulmonary vasculature at birth. Of the mediators or receptors in the question, adenosine triphosphate (ATP)–sensitive potassium channels likely play a crucial role in pulmonary vasodilation immediately after birth. Angiotensin II, leukotrienes, and type A endothelial receptors contribute primarily to pulmonary vasoconstriction. Although vascular endothelial growth factor (VEGF) has vasodilatory properties, it is primarily a mediator of angiogenesis and alveolarization in the developing lung.

In animal models, rhythmic lung expansion with a non-oxygen-containing gas mixture increases pulmonary blood flow by tethering open small pulmonary vessels. The sudden increase in pulmonary blood flow imposes a sheer stress on the endothelium which stimulates the release of vasoactive substances such as prostacyclin, prostaglandins, bradykinin, and nitric oxide (NO). The sudden increase in shear stress at birth coincides with an increase in NO and prostacyclin production, suggesting that the two agents act in concert to facilitate the vasodilatory changes. The effects of vasoactive substances likely vary in different segments of the pulmonary artery and the predominant mechanism in each segment may change as the lung matures. Furthermore, dilation of the pulmonary arteries rather than pulmonary veins is believed to be primarily responsible for the postnatal fall in PVR. However, recent evidence suggests that dilation of the pulmonary veins may play a role.

Mechanisms of oxygen-induced pulmonary vasodilation at birth are not fully understood, especially in humans, and conflicting data have been obtained from animal models. In
Experimental animals, pulmonary vascular tone appears to be regulated by a balance between endothelium-derived mediators that have vasodilatory effects (NO, endothelial-derived hyperpolarizing factor [EDHF], and prostacyclin), and a few potent vasoconstrictors (endothelin-1 [ET-1] and leukotrienes). Prostaglandins contribute to the pulmonary vasodilation during lung inflation but appear to contribute little to the dilatory changes induced by oxygen. NO is clearly involved in the postnatal fall in PVR in rats and sheep. However, in a recent study of spontaneously aborted human fetuses, endothelial NO synthase (eNOS) expression (eNOS) expression fell during the alveolar stage of lung development and after birth. Furthermore NO-dependent vasodilation after acetylcholine stimulation is absent at birth in newborn piglets and eNOS-deficient mice survive, suggesting that the NO pathway is not essential for the initial oxygen-induced pulmonary vasodilation seen immediately after birth. The discrepancy between the decrease in eNOS expression and the onset of marked vasodilation after birth suggest that vasoactive factors other than NO may mediate oxygen-induced changes in PVR immediately after birth.

Endothelial-derived hyperpolarizing factor may play a role in oxygen-induced pulmonary vasodilation through activation of potassium (K+) channels. Different types of potassium channels have been described in smooth muscle. K+ channels have been implicated as sensors or effectors for oxygen-induced changes in pulmonary vascular tone.

Although the roles of the various potassium channels are being investigated, oxygen-induced pulmonary vasodilation is inhibited by blocking K+Ca and K+ATP channels in near-term fetal lambs. In lung tissue from spontaneously aborted fetuses, K+ATP channels were strongly expressed in the smooth muscle of near-term fetuses and newborns, suggesting that these channels may play a role in human pulmonary vascular adaptation at birth. Changes in K+ channel activity may occur from a direct effect of oxygen tension on the channels, or alternatively the channels may open in response to changes in cellular redox potential or changes in concentration of second messenger substances such as NO, cyclic adenosine monophosphate, or prostacyclin.

The opening of K+ATP channels in newborn lambs and piglets, and associated pulmonary vasodilation, can partially be inhibited by factors derived from the endothelium. ET-1, a peptide produced by vascular endothelial cells, causes pulmonary vasoconstriction in the fetus and newborn by activating type A endothelin receptors (ET_A) on smooth muscles. ET-1 can also cause pulmonary vasodilation by activating type B endothelin receptors (ET_B) on endothelial cells. Vascular smooth muscle relaxation induced through K+ATP channels is accentuated by ET-A receptor blockade. Endothelial ET_B receptors mediate vasodilation through release of NO or prostacyclin, or by opening K+ATP channels. ET-B expression increases at mid-term and remains high until birth, suggesting that it may have an important role in pulmonary vasodilation after birth. Expression of ET-A is relatively stable throughout gestation. The Figure summarizes many of the pathways involved in regulation of pulmonary vascular tone in the fetus and neonate.

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The fetal pulmonary endothelium produces vasodilators, but vasoconstrictors such as ET-1 and leukotrienes predominate. The fetal vasculature readily opposes vasodilation. Angiotensin II is a powerful vasoconstrictor of pulmonary vascular smooth muscle cells. Angiotensin acts to increase ET-1 production, which is responsible for the vasoconstrictive effects it has on the pulmonary vascular bed. Angiotensin II is formed from angiotensin I by angiotensin-converting enzyme. Angiotensin is first expressed in the endothelium of the large proximal pulmonary arteries in the pseudoglandular phase of lung development and then it extends to the distal arteries during gestation. Expression of angiotensin-converting enzyme is lower at birth than in mature animals.
The release of VEGF from the airway epithelium helps to control pulmonary vascular formation by directing endothelial cell migration, vascular assembly, and subsequent alignment of the distal epithelium and vascular bed. Although VEGF is crucial for normal animal lung development, human data are sparse. In humans, VEGF expression increases between the canalicular and saccular stages of lung development and then drops off sharply during the alveolar stage. The higher endothelial permeability is noted in fetal life probably in part because of VEGF, which acts as a potent inducer of plasma extravasation in the fetal lung.

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References:


American Board of Pediatrics Content Specification(s):

Understand the factors affecting and regulating systemic circulation in the fetus and newborn infant and during the transitional period

Understand the factors affecting and regulating the pulmonary circulation in the fetus and newborn infant and during the transitional period
January

A woman is in preterm labor at 26 weeks’ gestation; she received betamethasone 3 days ago. Her first pregnancy ended at 28 weeks’ gestation following a precipitous vaginal delivery en route to the hospital. Despite stabilization with surfactant given 10 minutes after birth and low ventilator and oxygen support, the infant died at 2 hours of age from air leaks into the pleural and pericardial spaces after a mechanical failure of the ventilator. During your discussion, the woman and her husband ask if there is any way to avoid the use of mechanical ventilation if their infant were to be born today. You discuss strategies for delivery room resuscitation, and, if needed, use of continuous positive airway pressure, surfactant, and mechanical ventilation.

Of the following, the resuscitation strategy in very-low-birthweight preterm infants that has been found to be MORE frequently complicated by pneumothorax than intubation and mechanical ventilation is:

- A. high-flow nasal cannula
- B. intubation/surfactant/rapid extubation
- C. nasal continuous positive airway pressure
- D. nasal intermittent positive pressure ventilation
- E. prophylactic surfactant/mechanical ventilation

**Incorrect:**
Correct Answer: C

A number of strategies for resuscitating preterm infants at high risk for respiratory distress syndrome (RDS) in the delivery room have been or are being investigated. Of the delivery room options cited, nasal continuous positive airway pressure (CPAP) is associated with increased risk of air leak compared with intubation and mechanical ventilation.

Exposure of the fetus to antenatal corticosteroids and postnatal surfactant replacement independently and additively increase survival, reduce the incidence and severity of RDS, and reduce the incidence of air leaks in preterm infants born between 23 and 29 weeks of gestation (Table 1). Intracranial hemorrhage also is less frequent after antenatal exposure to corticosteroids (Table 2). Despite improvement in some outcomes, this risk of bronchopulmonary dysplasia is not changed by antenatal corticosteroids or surfactant replacement.
Table 1: Antenatal Corticosteroids, Postnatal Surfactant, and Outcomes*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Antenatal Corticosteroids</th>
<th>No Antenatal Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surfactant (N = 57)</td>
<td>No surfactant (N = 46)</td>
</tr>
<tr>
<td>Death, %</td>
<td>0</td>
<td>6.5</td>
</tr>
<tr>
<td>Pneumothorax, %</td>
<td>1.7</td>
<td>13.0</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia, %</td>
<td>49.0</td>
<td>55.3</td>
</tr>
<tr>
<td>Grade 3 or 4 intraventricular hemorrhage, %</td>
<td>6.9</td>
<td>10.9</td>
</tr>
</tbody>
</table>

* Adapted from Jobe et al (1993).

Table 2: Antenatal Steroids and Outcomes*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>Antenatal Steroids</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress syndrome, %</td>
<td>24</td>
<td>16</td>
<td>0.53 (0.44-0.63)</td>
</tr>
<tr>
<td>Surfactant use, %</td>
<td>21</td>
<td>10</td>
<td>0.41 (0.18-0.89)</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>12</td>
<td>7</td>
<td>0.60 (0.48-0.75)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage, %</td>
<td>26</td>
<td>16</td>
<td>0.48 (0.32-0.72)</td>
</tr>
</tbody>
</table>

* Adapted from Crowley P. Cochrane Database Syst Rev. 2003;3.

An important advance in the care of preterm infants would be to reduce the incidence of bronchopulmonary dysplasia and of the associated long-term neurologic, developmental, and pulmonary morbidities. Because exposure to positive pressure ventilation is a significant risk factor for the development of bronchopulmonary dysplasia, delivery room and ongoing care strategies to eliminate or limit exposure to positive pressure ventilation have been subjects of intense investigation.

The anticipated incidence of severe RDS in low-birthweight infants ranges from 50% to 70%, and is inversely proportional to birthweight (Table 3).

Table 3: Incidence of Severe Respiratory Distress Syndrome (RDS) by Birthweight*

<table>
<thead>
<tr>
<th>Birthweight, g</th>
<th>RDS, severe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>600-750</td>
<td>70%</td>
</tr>
<tr>
<td>751-1000</td>
<td>56%</td>
</tr>
<tr>
<td>1001-1250</td>
<td>51%</td>
</tr>
</tbody>
</table>

* Adapted from Crowley P. Cochrane Database Syst Rev. 2003;3.
Support for delivery room administration of CPAP includes:

- High compliance with administration of corticosteroids to women at high risk for preterm delivery (70% to 95% of eligible cases receiving treatment)
- Documented efficacy of antenatal corticosteroids to reduce RDS, air leaks, and mortality
- Large clinical experiences and small randomized trials showing success in stabilizing some spontaneously breathing preterm infants with signs of RDS using CPAP in the delivery room; success is inversely proportional to gestational age.

Morley and associates evaluated delivery room interventions among a group of infants born at 25 to 28 weeks’ gestation, 94% of whom had the benefit of antenatal steroid exposure. The study group of breathing infants received nasal CPAP of 8 cm H<sub>2</sub>O after initial resuscitation in the delivery room. The control group received intubation and mechanical ventilation after initial resuscitation. Surfactant was given only to infants who underwent intubation, and surfactant use was not controlled in the study. The only statistically significant differences between the nasal CPAP group and the group receiving mechanical ventilation included an increased incidence of pneumothorax, 9% versus 3% (<i>P</i> = .001), respectively. Other findings included lower use of surfactant; increased use of methylxanthines; and a lower median number of days of intubation and mechanical ventilation (Table 4).

Table 4: Continuous Positive Airway Pressure (CPAP) or Intubation/Mechanical Ventilation and Outcomes in Infants at 25 to 28 Weeks’ Gestation*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CPAP (N = 307)</th>
<th>Mechanical Ventilation (N = 303)</th>
<th>Odds Ratio (95% Confidence Interval) or P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (before 36 weeks’ postmenstrual age), %</td>
<td>6.5</td>
<td>5.9</td>
<td>1.10 (0.57-2.12)</td>
</tr>
<tr>
<td>Death or oxygen treatment at 36 weeks’ postmenstrual age, %</td>
<td>33.9</td>
<td>38.9</td>
<td>0.80 (0.58-1.12)</td>
</tr>
<tr>
<td>Pneumothorax, %</td>
<td>9.1</td>
<td>3.0</td>
<td>.001</td>
</tr>
<tr>
<td>Pulmonary interstitial emphysema, %</td>
<td>5.5</td>
<td>3.6</td>
<td>0.33</td>
</tr>
<tr>
<td>Surfactant treatment, %</td>
<td>38</td>
<td>77</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Methylxanthine use, %</td>
<td>84</td>
<td>71</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any ventilatory support (median days), %</td>
<td>21</td>
<td>26</td>
<td>0.24</td>
</tr>
<tr>
<td>Intubation/mechanical ventilation (median days), %</td>
<td>3</td>
<td>4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oxygen (median days), %</td>
<td>42</td>
<td>49</td>
<td>0.07</td>
</tr>
<tr>
<td>Grade 3 or 4 intraventricular hemorrhage, %</td>
<td>8.9</td>
<td>9.3</td>
<td>0.89</td>
</tr>
<tr>
<td>Length of hospital stay (median days), %</td>
<td>74</td>
<td>78</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* Adapted from Morley et al (2008).

It is plausible that the significantly reduced use of surfactant among those infants with RDS randomized to the nasal CPAP arm may have contributed to heterogeneous distribution of ventilation and to the air leaks.

A resuscitation strategy that combines the benefits of prophylactic surfactant administration and nasal CPAP is described as INVutation, SURfactant administration, and Rapid EXTubation.
to nasal CPAP, or INSURE. Compared with a strategy of intubation, rescue surfactant treatment, and continued mechanical ventilation, the INSURE strategy has been studied in a number of small randomized controlled trials, six of which have been included in a systematic review (Table 5).

**Table 5: Prophylactic/Early Surfactant with Rapid Extubation to Nasal Continuous Positive Airway Pressure (NCPAP) versus Continued Mechanical Ventilation and Rescue Surfactant (Surf; 91% ≥ 29 Weeks’ Gestation or > 1,250 g Birthweight)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prophylactic/Early Surf + NCPAP</th>
<th>Rescue Surf + Continued Ventilation</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation</td>
<td>125/335 (37%)</td>
<td>183/329 (56%)</td>
<td>0.67 (0.57-0.79)</td>
</tr>
<tr>
<td>Air leaks</td>
<td>14/335 (4%)</td>
<td>27/329 (8%)</td>
<td>0.52 (0.28-0.96)</td>
</tr>
<tr>
<td>Oxygen at 28 days</td>
<td>10/132 (8%)</td>
<td>20/130 (15%)</td>
<td>0.51 (0.26-0.99)</td>
</tr>
<tr>
<td>Death by 28 days</td>
<td>3/198 (1.5%)</td>
<td>7/198 (3.5%)</td>
<td>0.52 (0.17-1.56)</td>
</tr>
<tr>
<td>Surfactant</td>
<td>131/132 (99%)</td>
<td>79/130 (61%)</td>
<td>1.62 (1.41-2.86)</td>
</tr>
<tr>
<td>Mean surfactant doses per case</td>
<td>1.09-1.3</td>
<td>0.55-0.8</td>
<td>0.57 (0.44-0.69)</td>
</tr>
</tbody>
</table>

* Adapted from Stevens et al (2007).

More than 90% of infants included in these trials were born after 29 weeks of gestation or at birthweights of more than 1,250 g. In this group of older and larger infants, the INSURE group, which had undergone extubation to nasal CPAP, had a significantly lower incidence of air leaks than did the rescue surfactant/mechanical ventilation group (4% versus 8%). Furthermore, the need for mechanical ventilation (37% versus 56%) and oxygen treatment 28 days after birth (8% versus 15%) was significantly reduced. In a group of infants born at 27 to 31 6/7 weeks of gestation (n = 278), the INSURE strategy was compared with a control group resuscitated with CPAP alone, with surfactant replacement provided based on clinical indicators. The INSURE strategy significantly reduced the incidence of air leaks (2% versus 9%; relative risk, 0.25; 95% confidence interval, 0.07-0.85; number needed to treat, 11)] and the need for mechanical ventilation. No differences in death, bronchopulmonary dysplasia, or severe intraventricular hemorrhage were found. Such results suggest that the INSURE strategy can reduce complications such as air leaks in this older and larger group of infants without an increase in death or important morbidities.

Tooley and Dyke reported a small controlled trial of extremely preterm infants born between 25 and 28 weeks of gestation, all of whom received prophylactic surfactant and were randomized 1 hour after birth to extubation to nasal CPAP or continued mechanical ventilation. Significantly fewer infants in the CPAP group received mechanical ventilation after 1 hour of age (62% versus 100%, P=.0034) and fewer infants underwent intubation by 72 hours of age (47% versus 81%, P=.025). No differences were found in the important outcomes of death, bronchopulmonary dysplasia, or severe intraventricular hemorrhage. No appropriately powered study of the INSURE strategy for resuscitation has yet reported efficacy at improving any of the most important outcomes in infants born at 29 weeks of gestation or less or at birthweights less than 1,250 g.

Prophylactic surfactant treatment for RDS is associated with lower rates of air leaks, mortality, and the combined outcome of bronchopulmonary dysplasia or death compared with control patients who received rescue surfactant for defined indications (Table 6).

**Table 6: Prophylactic or Very Early Surfactant and Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>Surfactant</th>
<th>Relative Risk (95% Confidence)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax, %</td>
<td>18</td>
<td>11</td>
<td>0.62 (0.42-0.89)</td>
</tr>
<tr>
<td>Pulmonary interstitial</td>
<td>23</td>
<td>8</td>
<td>0.54 (0.36-0.82)</td>
</tr>
<tr>
<td>emphysema, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, %</td>
<td>35</td>
<td>16</td>
<td>0.61 (0.48-0.77)</td>
</tr>
<tr>
<td>Bronchopulmonary</td>
<td>62</td>
<td>52</td>
<td>0.85 (0.76-0.95)</td>
</tr>
<tr>
<td>dysplasia or death, %</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from Soll and Morley (2001).

High-flow nasal cannula and nasal intermittent positive pressure ventilation for resuscitation and stabilization of preterm infants with respiratory distress in the delivery room have not been studied in clinical trials. Although high-flow nasal cannula has been applied to infants with mild respiratory distress and apnea, and to facilitate transition after extubation, little information about efficacy exists. Because high-flow cannula results in variable degrees of increased airway pressure similar to nasal CPAP, caution should be used when applied in clinical settings such as that described in the vignette. Similarly, nasal intermittent positive pressure ventilation has been investigated in short-term studies after extubation and for apnea—no data that are applicable to the setting in the vignette are reported. Caution similar to that used with high-flow cannula may be appropriate.

**References:**


Engle WA, the Committee on Fetus and Newborn. Surfactant-replacement therapy for respiratory distress in the preterm and term neonate. *Pediatrics.* 2008;121;419-432


Lemyre B, Davis G, De Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity [review]. *Cochrane Database of Sys Rev.* 2009;(1):CD002272


Stevens TP, Blennow M, Myers EH, Soll R. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Sys Rev.* 2007;(4):CD003063


**American Board of Pediatrics Content Specification(s):**

02_Asphyxia_Resuscitation: Know the proper approach to airway management in the delivery room

02_Asphyxia_Resuscitation: Know the indications for assisted ventilation immediately after birth and how to assess its effectiveness
02_Aspphyxia_Resuscitation: Understand how to use self inflating and flow inflating bags for providing assisted ventilation in the delivery room

04_Respiratory: Know the clinical strategies and therapies used to decrease the risk and severity of RDS

04_Respiratory: Know the indications for and techniques of continuous positive airway pressure (CPAP)
March

ASSESSMENT PROGRESS:  Total Questions: 10  Questions Answered: 6  Correct Answers: 0

Question 6

You are about to attend the vaginal delivery of a 600-g, 24-week-gestation infant following progressive preterm labor. The mother has been hospitalized for 3 days and has received betamethasone and magnesium sulfate. As you are aware of the high risks associated with this gestational age and birthweight, you contemplate using a volume-controlled ventilation strategy for this infant’s respiratory support.

Of the following, volume-controlled ventilation, as compared with pressure-controlled ventilation, in extremely-low-birthweight neonates, is MOST likely to yield:

- A. fewer grade III/IV intraventricular hemorrhages
- B. greater risk for chronic lung disease
- C. lower survival to hospital discharge
- D. more air leaks
- E. prolonged need for assisted ventilation

Incorrect:

Correct Answer: A

Several modes of conventional assisted ventilation are used to support extremely-low-birthweight (ELBW), low-gestational-age infants. The use of pressure-limited, time-cycled (PLTC) ventilation has been the most commonly used mode of assisted ventilation. Mechanical support is regulated by controlling peak inspiratory pressure, ratio of inspiratory to expiratory time (I:E ratio), ventilator rate, and positive end-expiratory pressure. Although not difficult to administer, use of PLTC ventilation has been associated with several difficulties:

- Variability in compliance and resistance of the patient airway (and of the ventilatory circuit) results in significant breath-to-breath fluctuations in tidal volume (Vt), with measured Vt exceeding desired Vt in one fourth of breaths and not reaching desired Vt in one third of breaths.
- As the ventilator rate is decreased, spontaneous patient breaths may be associated with excessive work of breathing.
- Asynchrony between administered and spontaneous breaths affects Vt, minute ventilation, and arterial pulse pressure.
As the ability to measure Vt and patient inspiratory effort became more available, modifications to PLTC ventilation included:

- Synchronization of patient effort and assisted breaths, with back-up ventilation rate for periods of apnea
- Assist-controlled ventilation, wherein patient-triggering initiates each breath, again with back up to cover apnea
- Pressure-support ventilation, wherein inspiratory support is provided until the inspiratory flow decreases to a preset level, thus enhancing synchrony between patient effort and ventilator assist.

Although these synchronization strategies have physiologic plausibility, clinical comparisons with the usual PLTC ventilation techniques have not demonstrated significant improvements in mortality, reduction in chronic lung disease (bronchopulmonary dysplasia), or improvements in other morbidities (air leaks, retinopathy, severe intraventricular hemorrhage). Of note, synchronization and patient triggering have been associated with trends toward shorter duration of ventilation; thus these approaches may offer some added benefit to the ELBW infant by decreasing exposure to the ventilator. Data to evaluate these infants are forthcoming.

Studies have demonstrated the rapidity and severity of lung injury associated with overdistention of the lung regardless of pressure, and technological advances have allowed Vt and patient effort to be more rapidly and accurately measured. With these changes, modes of ventilation have been developed which use volume control (VC) or volume targeting to prevent lung overdistention and its associated microvascular injury and potential for the development of chronic lung disease. Use of VC has been less extensive and, as with pressure control (PC) ventilation, experience in its use and monitoring is needed for optimal outcomes.

Caution is warranted regarding a wholesale shift of conventional ventilation to volume-regulated strategies pending more extensive experience in controlled settings and larger studies of outcomes, especially longer-term developmental status. A metaanalysis of four small randomized trials (178 low birthweight infants) comparing volume-controlled to pressure-controlled ventilation has reported the following:

- Fewer grade 3 and 4 intraventricular hemorrhages (relative risk [RR] = 0.32; 95% confidence interval [CI] = 0.11-0.90; number needed to treat [NNT] = 6)
- A possible trend toward reduction of bronchopulmonary dysplasia/chronic lung disease (RR = 0.34; 95% CI = 0.11-1.05)
- Reduction in air leaks (RR = 0.23; 95% CI = 0.07-0.76; NNT = 9)
- Shorter duration of assisted ventilation (weighted mean difference, 2.93 days; 95% CI = 4.28-1.57)
- No effect on mortality

Investigators have observed trends toward shorter periods of ventilation to reduce the alveolar-arterial oxygen gradient to less than 100 mm Hg and toward reduced mortality among a relatively small group of infants weighing 600 to 1,500 g at birth. These data suggest promise for volume targeted strategies.

References:


Related readings from Neoreviews.org


American Board of Pediatrics Content Specification(s):

04_Respiratory: Know the prenatal and postnatal risk factors for bronchopulmonary dysplasia/chronic lung disease and be aware of various preventive strategies

04_Respiratory: Know factors that determine residual lung volume, functional residual capacity, and tidal volume, and how they change with various pulmonary disorders

04_Respiratory: Know the effects and risks of PPV

04_Respiratory: Know the pathogenesis, pathophysiology, and pathologic features of bronchopulmonary dysplasia/chronic lung disease

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March

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Total Questions: 10  Questions Answered: 2  Correct Answers: 0

Question 2

A woman who is pregnant at 36 weeks’ gestation and her husband are discussing with you the risks of delivery before 39 weeks’ gestation. They have asked their obstetrician to perform a repeat cesarean in 1 week. The possibility of respiratory distress and admission for intensive care is raised. The woman asks what causes breathing problems in infants after 36 weeks’ gestation.

Of the following, the cause for severe respiratory distress that has MOST significantly decreased, with recent changes in the epidemiology of live births, is:

- A. meconium aspiration
- B. pneumonia
- C. pneumothorax
- D. respiratory distress syndrome
- E. transient tachypnea

Incorrect:
Correct Answer: A

In the United States, the gestational ages at births have seen dramatic shifts in the past two decades (Figure 1).

Figure 1: Percent distribution of births by gestational age in United States, 1990 and 2004 (from the Centers for Disease Control and Prevention, National Center for Health Statistics final natality data, 2004).
The average gestational age at birth is no longer 40 weeks; it is 39 weeks. This profound shift has been accounted for by a large increase in births at 34 to 39 weeks’ gestation and a large decrease in births after 40 weeks’ gestation (Table 1).

Many factors have likely contributed to the recent shift in gestational age at birth:

- Increased surveillance of pregnancies as evidenced by greater use of fetal ultrasonography and fetal heart rate monitoring
- Rising rates of maternal complications (such as preterm premature rupture of membranes and premature labor)
- Errors in gestational age assessment
- Increased multifetal pregnancies
- Parent or physician preference (increased elective inductions of labor and cesareans)
- Fear of late stillbirth (Figures 2 and 3)

Figure 2: Early delivery of high-risk mothers and infants at risk for fetal death between 1990 and 2000: decrease in late fetal deaths (>28 weeks)
The incidence of respiratory distress in neonates after birth has remained relatively stable but the incidence of major causes has changed. The incidence of meconium aspiration has declined significantly. In a population-based study in Australia and New Zealand between 1995 and 2002, the rate of meconium aspiration syndrome (respiratory distress, meconium-stained amniotic fluid, and mechanical ventilation) changed from 0.43 per 1,000 live births to 0.35 per 1,000 live births ($P=0.0087$). The incidence of meconium aspiration was lower because fewer infants were born after 40 weeks' gestation and the incidence of meconium aspiration syndrome in this same group of neonates was lower. Approximately one third of infants with meconium aspiration syndrome were born in the previous decade at 41 weeks' gestation or greater. The reasons for the decrease in incidence of meconium aspiration syndrome in infants born after 40 weeks' gestation are unclear. In mothers of infants with meconium aspiration syndrome, assisted vaginal births decreased from 16.1% of total births to 7.9% in the Australia–New Zealand experience, while cesarean deliveries increased slightly (41.8% to 47.1%). Accompanying these changes were a significantly lower proportion of infants with Apgar scores less than 7 at 5 minutes and requiring intubation in the delivery room. It could be speculated that subtle changes in obstetric triggers for cesarean deliveries (evidenced by greater pregnancy surveillance accompanied by significantly more reported pregnancy complications, greater frequency of non-reassuring fetal heart rate patterns diagnosed, and fewer emergency cesarean deliveries) and avoidance of vaginal deliveries using instruments accounted for a lower incidence of fetal distress and, subsequently, meconium aspiration.

The incidence of respiratory distress syndrome and transient tachypnea of the newborn has increased because of the shift to late preterm (34 0/7 to 36 6/7 weeks' gestation) and early
term (37 0/7 to 38 6/7 weeks’ gestation) births. Both of these groups have significantly higher risks for respiratory morbidity (transient tachypnea, respiratory distress syndrome, persistent pulmonary hypertension) than infants born at 39 to 40 weeks’ gestation (Table 2).

Table 2: Relative Risk of Respiratory Morbidity (Respiratory Distress Syndrome, Transient Tachypnea Of The Newborn, or Persistent Pulmonary Hypertension of the Newborn) by Gestational Age*

<table>
<thead>
<tr>
<th>Gestational Age, wk</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>35.1</td>
<td>17.1-71.9</td>
</tr>
<tr>
<td>35-36</td>
<td>5.3</td>
<td>2.6-10.5</td>
</tr>
<tr>
<td>37-38</td>
<td>1.6</td>
<td>0.9-3.1</td>
</tr>
<tr>
<td>39-40</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

* Adapted from Yoder et al (2008).

The rising proportion of births of late preterm and term infants by cesarean section also contributes to the higher incidence of respiratory morbidity because cesarean delivery increases the risk of respiratory disorders, especially transient tachypnea about threefold (4.4% versus 1.4%; odds ratio, 3.3; 95% confidence interval, 2.7-4.0).

The epidemiology of respiratory failure because of pneumonia and pneumothorax in late preterm and term neonates is not described. The proportion of neonates with pneumonia requiring mechanical ventilation is similar in early term (37-38 weeks’ gestation) and term (39-41 weeks’ gestation) infants (7%-8%). It is likely that a shift toward births before 41 weeks’ gestation will not change the incidence of pneumonia. Primary pneumothorax requiring mechanical ventilation occurs more often in infants born at 39 to 41 weeks’ gestation (4.8%) than in early term infants born at 37 to 38 weeks’ gestation (1.5%) but secondary pneumothorax occurs more frequently than primary pneumothorax and at earlier gestational ages (30.8% at 37-38 weeks’ gestation versus 15.6% at 39-41 weeks’ gestation). Among infants receiving mechanical ventilation for respiratory failure, the total incidence of pneumothorax, therefore, is 32.3% at 37 to 38 weeks’ gestation and 20.4% at 39 to 41 weeks’ gestation. If these data are representative of that incidence rate in other countries, an increase in early term births would increase the rate of pneumothorax as a contributing cause for respiratory failure. Because this estimate is based on limited data from a single region in France and may not be applicable to other sites, the true impact of pneumothorax on the epidemiology of respiratory distress in late preterm and term neonates remains unclear.

References:


Clark RH. The epidemiology of respiratory failure in neonates born at an estimated gestational age of 34 weeks or more. J Perinatol. 2005;25:251-257


**American Board of Pediatrics Content Specification(s):**

04_Respiratory: Know the pathophysiology and risk factors for RDS

04_Respiratory: Know the pathogenesis, pathophysiology, and risk factors of transient tachypnea of the newborn infant

04_Respiratory: Know the pathogenesis and causative agents in an infant in whom neonatal pneumonia is suspected

04_Respiratory: Know the pathogenesis, pathophysiology, pathologic features, and risk factors of meconium aspiration syndrome
Question 6

Figure: Depressed, nonvigorous neonate immediately after he was born through meconium-stained amniotic fluid.

A full-term infant is born through meconium-stained amniotic fluid (MSAF); he is limp and apneic immediately after birth. The physician suctions his trachea for meconium and then begins positive pressure ventilation for a heart rate of 80 beats per minute 30 seconds after birth. One minute after birth, his heart rate is 120 beats per minute, his respiratory rate is 50 breaths per minute, and his oxygen saturation in the right hand is 65% in room air.

Of the following, the MOST appropriate intervention at this time is to:

- A. initiate chest compressions
- B. intubate and suction the trachea again
- C. manage expectantly
- D. provide free flow oxygen
- E. provide positive pressure ventilation

Incorrect:
Correct Answer: C
The infant in the vignette demonstrated signs of an effective, although assisted, transition from fetal to neonatal existence. The heart rate and respiratory effort are normal as is the oxygen saturation for an infant 1 minute after birth. Observation and expectant management are indicated; he does not require any intervention at this time.

The infant in this vignette was born through meconium-stained amniotic fluid (MSAF) and he was limp and apneic; he was not vigorous. The initial response in this circumstance according to the Neonatal Resuscitation Program (NRP) guidelines is to intubate and suction the trachea. At 30 seconds, if the heart rate remains less than 100 beats per minute (bpm) or the respiratory effort is inadequate, positive pressure ventilation is the next recommended intervention. In this case, the infant responded well and had a heart rate greater than 100 (best indicator of effective positive pressure ventilation) and exhibited effective respiratory effort by 1 minute after birth. The preductal oxygen saturation was 65%, a normal value for infants at 1 minute of age.

In previous renditions of NRP, free flow oxygen was indicated for central cyanosis, but the amount of oxygen that should be delivered remained controversial. These concerns center on the potential adverse effects of 100% oxygen on respiratory physiology and cerebral circulation and the potential tissue damage from oxygen free radicals. Conversely there are also concerns about tissue damage from oxygen deprivation during and after asphyxia. Metaanalysis of four human studies demonstrated a reduction in mortality rate and no evidence of harm in infants resuscitated with room air versus 100% oxygen (the methods used in these studies have been questioned for poor randomization and inconsistent definitions of asphyxia).

It has been suggested that administration of a variable concentration of oxygen guided by pulse oximetry may improve the ability to achieve normoxia more quickly. Evidence obtained with continuous oximetry, however, has shown that neonatal transition is a gradual process. Investigators have only recently established data on the normal pulse oximetry values for full-term infants in the first few minutes after birth. In one investigation, 92 full-term infants were monitored with pulse oximetry immediately after birth. The median (interquartile range) saturation of peripheral oxygen (SpO2) at 1 minute was 63% (53%-68%). The SpO2 gradually rose with time, with median values reaching 90% at 5 minutes (79%-91%). For the infant in this vignette, an SpO2 of 65% one minute after birth is normal, and if it continues to rise he should not require supplemental oxygen.

Chest compressions are indicated if the heart rate remains less than 60 bpm after 30 seconds of effective positive pressure ventilation; the infant in this vignette never had a heart rate less than 60 bpm. Reintubation for meconium suction would not be indicated in an infant who had made the transition well. Free flow oxygen would not be indicated for the infant in the vignette because his SpO2 was within the normal range for age. Positive pressure ventilation was not indicated at this point either, because his heart rate was more than 100 bpm and he was demonstrating signs of effective respiratory effort.

References:


Kattwinkel J. Evaluating resuscitation practices on the basis of evidence: the findings at first glance may seem illogical. *J Pediatr.* 2003;142:221-222


Toth B, Becker A, Seelbach-Gobel B. Oxygen saturation in healthy newborn infants
immediately after birth measured by pulse oximetry. *Arch Gynecol Obstet.* 2002;266:105-107

*Additional readings from Neoreviews.org*

**American Board of Pediatrics Content Specification(s):**

02_Aspphyxia_Resuscitation: Know indications for and proper administration of supplemental oxygen in the delivery room
May

A woman presents for consultation at approximately 35 weeks' gestation. Her pregnancy has been uncomplicated, and she has no chronic medical conditions. However, with a previous pregnancy, she experienced a late third trimester fetal loss that was attributed to an umbilical cord accident. She is considering early induction of labor for the current pregnancy, but only if fetal lung maturity can be reasonably assured.

Of the following, the test for fetal lung maturity MOST directly measuring surfactant production is:

- A. fluorescence polarization
- B. foam stability index
- C. lamellar body count
- D. lecithin/sphingomyelin ratio
- E. phosphatidylglycerol concentration

Incorrect: C

Pulmonary immaturity resulting in neonatal respiratory distress syndrome (RDS) contributes substantially to the morbidity and mortality experienced by the infant born prematurely. Improved obstetrical dating using ultrasonography and the use of antenatal steroids to accelerate fetal lung maturity have decreased the incidence of RDS. However, infants born in the late preterm period remain at higher risk of respiratory morbidity than those born at term, and infants born at 37 weeks' gestation are at higher risk than those born at 39 weeks' gestation. When fetal maturity cannot be inferred from obstetric dating, RDS resulting from a scheduled delivery at less than 39 weeks' gestation may be reduced with the assessment of fetal lung maturity.

Maturation of the fetal lung is reflected by the presence of functional surfactant in the alveolar space. Type II pneumocytes line the alveoli and produce the surface-active phospholipid compounds comprising surfactant. Fetal respiratory activity during the latter portion of gestation permits the passage of surfactant into the amniotic fluid. Using amniocentesis, amniotic fluid can be sampled to assess fetal lung maturation.

Tests of fetal lung maturity assess either the concentration of pulmonary...
surfactant (biochemical tests) or the surface-active effects of these bioactive phospholipids (biophysical tests). Common tests of fetal lung maturity are phosphatidylglycerol presence, lecithin/sphingomyelin (L/S) ratio, fluorescence polarization (surfactant-to-albumin ratio), and lamellar body counts. The foam stability index (FSI) is used less frequently.

Among the available tests for fetal lung maturity, the lamellar body count most directly measures in utero surfactant production. Within the cytoplasm of type II pneumocytes, surfactant is stored in the form of lamellar bodies, which are actively secreted into the alveolar space and pass into the amniotic fluid (Figure).

**Figure: Type 2 pneumocyte demonstrating lamellar bodies (solid arrow) and surfactant extrusion (dashed arrow)**

Because lamellar body size is similar to that of platelets, standard hematologic counters can be used to quantify the presence of lamellar bodies in amniotic fluid. Fetal lung maturity is suggested by lamellar body counts of 50,000/μL or greater, whereas counts less than 15,000/μL suggest pulmonary immaturity. This measure is simple, inexpensive, and rapid. Meconium and blood contamination can falsely elevate the count. A lack of established protocols, consistent instrumentation, or consensus on cutoff values confounds the usefulness of this test.

The L/S ratio is one of the oldest tests of fetal lung maturity, and is based on the observation that in fetal pulmonary secretions, the concentration of lecithin (phosphatidylcholine) increases after 32 to 33 weeks’ gestation. Although pulmonary surfactant contains many phospholipids, lecithin is the major constituent in the mature compound. Sphingomyelin is used as the normalizing factor in the L/S ratio, because it has chromatographic similarity to lecithin and its concentration remains relatively constant in amniotic fluid in the third trimester. Neonatal RDS is uncommon when the L/S ratio is 2.0 or higher (usually around 35 weeks’ gestation) in uncomplicated pregnancies. Consequently, measurement of the L/S ratio, using thin-layer chromatography, provides a measure of fetal lung maturity. A value of 2.0 is the commonly accepted standard indicator of pulmonary maturity, but laboratories may vary in their cutoff. This technique is costly, requires highly trained personnel, and has a 4- to 6-hour turnaround time. Blood and meconium contamination interfere with interpretation of the test.

The FSI is based on the surface tension–lowering property of surfactant. No assumptions are made about surfactant composition; rather the assay relies on the ability of surfactant to generate stable foam in the presence of ethanol. This test is also known as the rapid surfactant test, the shake test, or the bubble stability test. The admixture of ethanol and amniotic fluid interferes with all but the physiologic lung surfactant in producing stable foam at the air-liquid interface. Aliquots of amniotic fluid (0.5 mL) are added to wells in a test kit containing serial dilutions of ethanol, and the mixtures are then shaken. In the presence of surfactant, a stable ring of foam is evident with the addition of 100% ethanol. The FSI is read as the highest value recorded in the well in which a stable ring of foam persists.
Fluorescence polarization uses polarized light to quantify the competitive binding of a probe to both albumin and surfactant in amniotic fluid. Because this method measures aggregate amounts of lecithin, sphingomyelin, phosphatidylglycerol, and phosphatidylinositol, it is a direct measurement of surfactant concentration. Net polarization values are high when the probe is bound to albumin. Conversely, net polarization values are low when the probe is bound to surfactant. When applied to amniotic fluid samples, the fluorescence polarization measured by an automated analyzer reflects the ratio of surfactant to albumin. An elevated ratio correlates with fetal lung maturity. Typically requiring 1 mL of amniotic fluid, a simple, automated, rapid test is available; assays vary minimally among laboratories. A commercial version of this assay (TDx-FLM II [Abbott Laboratories, Abbott Park, IL]) is widely available. Applying TDx-FLM II, values above 55 mg surfactant per 1 g of albumin are considered mature; values below 40 mg surfactant per 1 g of albumin are considered immature; and values in between are considered indeterminate. Blood and meconium contamination interfere with interpretation of the assay.

Phosphatidylglycerol is a minor constituent of surfactant and is measurable in amniotic fluid in increasing amounts several weeks after the rise in lecithin. The presence of phosphatidylglycerol can be determined by means of thin-layer chromatography or a slide-agglutination test using specific antiserum samples. The relatively quick slide-agglutination test is not affected by the presence of blood, meconium, or other amniotic fluid contaminants. Because phosphatidylglycerol appears late in gestation, when the incidence of RDS is low, the false-positive rate for the test is high. Similarly, when phosphatidylglycerol is absent, the risk of RDS is in the range of 25%.

Fetal lung maturity testing is better at predicting the absence of RDS, rather than the presence of RDS (Table).

<table>
<thead>
<tr>
<th>Test</th>
<th>Threshold for Maturity</th>
<th>Predictive Value for Pulmonary Maturity (%)</th>
<th>Predictive Value for Pulmonary Immaturity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamellar body count, /μL</td>
<td>&gt; 50,000</td>
<td>97-98</td>
<td>29-35</td>
</tr>
<tr>
<td>Lecithin/sphingomyelin ratio</td>
<td>&gt;2.0</td>
<td>95-100</td>
<td>33-50</td>
</tr>
<tr>
<td>Foam stability index</td>
<td>&gt;47</td>
<td>95</td>
<td>51</td>
</tr>
<tr>
<td>Phosphatidylglycerol</td>
<td>Present</td>
<td>95-100</td>
<td>23-53</td>
</tr>
<tr>
<td>Fluorescence polarization, surfactant mg/g albumin</td>
<td>≥55</td>
<td>96-100</td>
<td>47-61</td>
</tr>
</tbody>
</table>

*Adapted from ACOG Practice Bulletin (2008).

Overall, these tests yield high sensitivity for RDS (proportion of immature test result in neonates with RDS) and have high negative predictive values (probability of no RDS with a mature fetal lung maturity test result). No test has conclusively demonstrated superiority, and all perform less well at earlier gestational ages. Moreover, the positive predictive value of a test (probability of RDS when test result suggests pulmonary immaturity) will vary with the prevalence of RDS in the population sampled, and therefore decrease with advancing gestational age.

The American College of Obstetricians and Gynecologists recommends confirmation of fetal lung maturity before elective delivery at less than 39 weeks’ gestation, unless gestational age can be confirmed by obstetric history (2008). However, debate continues over the benefit of testing for fetal lung maturity after 36 weeks’ gestation. Because of the very minimal risk of RDS in this population, even a test with extremely high sensitivity and specificity would have relatively poor predictive value. In addition, amniocentesis is not without risks, documented at 0.7% in one study. Risks include preterm labor, premature rupture of membranes, placental abruption, and fetal-maternal hemorrhage. Furthermore, cost-effectiveness of testing for fetal lung maturity at more advanced gestational ages has
yet to be demonstrated.

**References:**


**Related readings from Neoreviews.org**


**American Board of Pediatrics Content Specification(s):**

01_Maternal_Fetal: Know the indications for and interpretation of tests of fetal lung maturity
June

A fellow pediatrician asks you to see an infant who has just been admitted to the neonatal intensive care unit. The 32-week-gestation boy has been delivered vaginally, precipitously, and after only one maternal dose of betamethasone. The pediatrician has been able to start mechanical ventilation and obtain a chest radiograph (Figure 1).

Figure 1: From Warren and Anderson (2009)

Surfactant has not been given. You find the infant in obvious respiratory distress, with tachypnea and deep retractions. A quick look at a pressure-volume pulmonary mechanics displayed on the
ventilator screen causes you to increase one ventilator setting. The infant then breathes easier.

Of the following, the pulmonary mechanics displayed on the ventilator screen was MOST likely to have been:

- A. Volume
- B. Volume
- C. Volume
- D. Flow
- E.
Correct

The infant in this vignette has clinical and chest radiographic features consistent with the diagnosis of respiratory distress syndrome (RDS). The pressure-volume loop displayed on the ventilator screen was most likely to have been the one shown in graphic C.

Graphic C: Pressure-volume loop showing an opening-pressure effect

This loop shows the opening-pressure effect associated with a low functional residual capacity (FRC), an effect commonly seen in infants receiving mechanical ventilation who have RDS. The maneuver that corrected the opening-pressure effect was an increase in the ventilator positive end-expiratory pressure (PEEP), resulting in an increase in FRC and more comfortable breathing. Graphics A, B, D, and E represent problems that, if seen in an infant with RDS, would be less likely to be corrected by any increase in a ventilator setting.

Graphic A: Pressure-volume loop showing “beaking,” suggesting excessive inspiratory pressure
Graphic B: Pressure-volume curve showing less expiratory volume than inspiratory volume, suggesting an air leak around the endotracheal tube. The dashed line is added by the ventilator software.

Graphic D: Flow-volume loop showing an erratic exhalation curve, suggesting condensate or other fluids in the ventilator tubing.

Graphic E: Flow-volume loop showing the “scooping” of flow limitation, suggesting small-airway obstruction.
Real-time ventilator display loops can be helpful in the treatment of infants receiving ventilator support, and can be especially helpful in identifying certain problems with mechanical ventilation. The normal pressure-volume loop (Figure 2) can be examined for its overall slope to give an indication of the total dynamic compliance. The hysteresis (width or "fatness") of the loop is often used as a surrogate for the dynamic airway resistance.

**Figure 2: Normal pressure-volume loop**

![Normal pressure-volume loop](image)

The normal flow-volume loop (Figure 3) has a straight-line portion during expiration. Because flow is the first derivative of volume, this straight line represents an exponential decay and can be used to derive the time constant of the respiratory system, the product of the dynamic compliance, and the dynamic resistance.

**Figure 3: Normal flow-volume loop**

![Normal flow-volume loop](image)
The infant in this vignette has a chest radiograph that shows air-bronchograms and a ground-glass appearance to the lung fields, strongly suggestive of RDS (Figure 1). In infants with RDS, the small airways collapse at end-expiration, causing a low FRC. Expansion of the collapsed airways is associated with the "crackles" heard on inspiration. The extra effort needed to open these collapsed airways at the start of inspiration is seen in the opening-pressure effect, in which the initial increase in airway pressure does not immediately cause an increase in volume. The answer to this effect is to raise the ventilator PEEP. By increasing the PEEP, the airways are splinted open, do not collapse, and are ready to expand immediately at the beginning of the next inspiration. Surfactant administration is another treatment that counters airway collapse at end-expiration.

An infant with RDS could have a ventilator display similar to that seen in graphic A. This pressure-volume loop shows "beaking," which suggests an excessive inspiratory pressure. At end-inspiration, the additional excessive pressure no longer causes as large a volume increase as at the start of inspiration. A decrease in the inspiratory pressure may be appropriate.

An infant with RDS could have a ventilator display similar to that seen in graphic B. This pressure-volume loop shows less expiratory volume than inspiratory volume, suggesting a leak around the endotracheal tube. If the ventilator flow rate is set too low, a large air leak might prevent the ventilator from achieving its assigned peak pressure or volume, but most ventilators can overcome the small leak indicated by graphic B.

An infant with RDS could have a ventilator display similar to that seen in graphic D. This flow-volume loop shows an erratic expiratory phase, and is most often caused by condensate or other fluids as they slosh around and are buffeted about in the ventilator tubing. Although this pattern can be seen in RDS, it is rarely the cause of distress to the infant, and no increase in any ventilator setting is likely to correct it. The solution is to drain the fluid.

The flow-volume curve of graphic E shows “scooping,” or flow limitation, on exhalation. This pattern is seen in asthma, bronchopulmonary dysplasia, and adult chronic obstructive pulmonary disease. It is unlikely to be seen in RDS. This pattern is thought to represent an obstruction to airflow at the level of the 1 mm distal airway. The shape of the “scooping” may indicate a disruption in the normal fractal pattern of the branching of the small airways.

**References:**


**Related readings from Neoreviews.org**


**American Board of Pediatrics Content Specification(s):**
04_Respiratory: Know the interpretation and limitations of methods for measuring pulmonary function

04_Respiratory: Recognize the clinical, imaging, and laboratory features of RDS

04_Respiratory: Plan the ventilatory therapy for infants with respiratory failure of different etiologies
July

A full-term female infant with a birthweight of 3.5 kg was delivered by caesarean section. Physical examination findings were normal. Four hours after delivery, the infant developed progressively worsening respiratory distress requiring intubation and assisted ventilation. Diagnostic workup confirmed group B Streptococcus (GBS) sepsis and pneumonia. Chest radiography was performed (Figure 1).

Figure 1
The infant’s condition gradually improved in the subsequent days and she underwent extubation on the 8th day after birth. However, increasing respiratory distress necessitated assisted ventilation 7 hours later. Chest radiograph obtained after intubation is presented in Figure 2.

![Figure 2](image_url)

The findings shown in Figure 2 were unchanged 2 days later.

Of the following, the MOST appropriate next step in the care of the infant in the vignette is:

- A. chest computed tomography
- B. chest physical therapy
- C. chest ultrasonography
- D. fluoroscopy
- E. thoracentesis

Incorrect: Correct Answer: C
The infant in the vignette has early-onset group B Streptococcus (GBS) sepsis and pneumonia. The initial chest radiograph showed evidence of perihilar streaking without focal consolidation of the lungs and normal position of diaphragm (Figure 1). The infant responded to appropriate treatment and was weaned off cardiorespiratory support by the 8th day after birth. Respiratory deterioration prompted intubation and reinstitution of assisted ventilation. The chest radiograph at this time showed marked opacification of the right hemithorax with shift of the mediastinum to the left (Figure 2). The differential diagnosis of this opacity includes atelectasis, pleural effusion, consolidation, and diaphragmatic eventration or herniation.

An association between neonatal GBS sepsis and delayed presentation of right-sided diaphragmatic hernia (DH) has previously been described. The diagnosis is prompted by the onset of sudden secondary respiratory deterioration during the recovery phase of neonatal GBS sepsis accompanied by persistent right-sided opacity on chest radiography. The diagnosis can be confirmed on chest ultrasonography (Figure 3).

**Figure 3: Longitudinal right upper quadrant scan showing herniation of liver through diaphragmatic defect (white arrows). The intact portion of the diaphragm is indicated by white arrowheads.**

Typical findings on chest ultrasonography include herniation of the liver into the right hemithorax, lack of visualization of superior portion of right hemidiaphragm (Figure 3), and paradoxical movement of the liver with respiration.

Group B beta-hemolytic *Streptococcus* infection is an important cause of neonatal pneumonia and sepsis. Delayed presentation of right-sided DH in association with GBS sepsis was first described by Kirchner et al in 1975. Most neonates with late-onset DH in association with GBS sepsis reported in literature are male with a median gestational age of 37 weeks and median postnatal age at diagnosis of 11 days. In the cases described, most of the neonates were showing improvement with antibiotics given for GBS sepsis, and then they experienced a sudden deterioration in respiratory status, associated with haziness or opacification of right lower lung fields on chest radiography. Therefore, the combination of GBS sepsis and persistent right-sided opacity on radiologic examination should alert one to look for the presence of right DH. In most cases described in literature, the diagnosis of DH was confirmed following thoracentesis, arteriography, peritoneography, fluoroscopy, computed tomography, thoracotomy, or autopsy. However, since the availability of ultrasonography, it has become possible to make the diagnosis of DH associated with GBS sepsis noninvasively and without the need to transport a sick newborn infant.

The differential diagnosis of opacification of the lung fields includes atelectasis, pleural effusion, consolidation, and diaphragmatic eventration or herniation. Atelectasis is associated with opacification of lung fields, volume loss, concave margin of the opacified region, and shift of the mediastinum toward the side with atelectasis. Figure 2 shows a convex margin of the opacified region with a mediastinum shift to the opposite side, thus making atelectasis an
unlikely diagnosis. Chest physical therapy, therefore, is unlikely to be helpful.

Although isolated pleural effusions often may be identified in patients with GBS pneumonia, the fluid accumulation is usually small and insufficient to warrant thoracentesis. In contrast, right-sided diaphragmatic hernia often occurs with a large pleural effusion because of obstruction of hepatic venous outflow and transudative weeping from the liver surface. Therefore, the development of an unexpectedly large pleural effusion may obscure the shadow of an abnormal diaphragm or abnormally elevated liver, and should alert the clinician to the possibility of an underlying diaphragmatic defect. Ultrasonography is a precise, noninvasive, and rapid diagnostic tool that distinguishes between DH and pleural fluid at the bedside. Thoracentesis without additional imaging studies to confirm the diagnosis can result in liver injury. Thoracentesis is contraindicated unless an ultrasound examination has been performed to exclude DH. Computed tomography will yield the correct diagnosis but is unnecessary. The diagnosis can be made with ultrasonography at the bedside, without transfer from the neonatal intensive care unit and with no exposure to radiation.

Eventration of the diaphragm may also present as opacification of the lung fields. In such cases, fluoroscopy may be helpful in evaluating the position and movement of the lungs and diaphragm with respiration. However, diaphragmatic defects are not visualized on fluoroscopy. Although early-onset GBS sepsis has been associated with delayed-onset DH, such an association has not been reported for diaphragmatic eventration. Therefore, fluoroscopy would not be helpful in the infant in this vignette.

The reason for delayed presentation of right DH in association with GBS sepsis is unknown but several pathophysiologic mechanisms have been hypothesized. One theory is that GBS infection causes necrosis and destruction of the diaphragm resulting in an acquired herniation. However, others believe that the right-sided hernia is probably congenital, with the defect initially covered by the liver. Dysfunctional movements of the congenitally defective diaphragm predispose the infant to the development of pneumonia. In addition, as a result of the inflammatory process in the lungs from GBS pneumonia as well as the positive pressure from mechanical ventilation, the defect in the diaphragm does not manifest immediately. As the clinical condition of the neonate improves and both inflammation and mechanical ventilation are reduced, the liver and other intra-abdominal contents can herniate through the defect.

The overall survival of neonates with GBS sepsis and delayed presentation of DH after surgical intervention has been reported to be excellent despite significant respiratory compromise at presentation. This probably relates to the comparatively short postnatal period of intrathoracic herniation and the absence of significant developmental lung hypoplasia that usually complicates early-onset congenital DH.

References:


Related readings from Neoreviews.org

American Board of Pediatrics Content Specification(s):

10_Infectious_diseases: Know the clinical manifestations, laboratory features, and differential diagnosis of neonatal sepsis

10_Infectious_diseases: Understand the treatment and complications of sepsis

10_Infectious_diseases: Know the infectious agents that cause neonatal sepsis

04_Respiratory: Know the pathogenesis and causative agents in an infant in whom neonatal pneumonia is suspected

04_Respiratory: Plan the clinical, imaging, and laboratory features and the management of an infant in whom neonatal pneumonia is suspected

04_Respiratory: Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress

04_Respiratory: Recognize the clinical features of extrapulmonary causes of respiratory distress

04_Respiratory: Recognize the imaging features of extrapulmonary causes of respiratory distress
Question 2

You receive a message from the obstetrics department that a woman who is 25 weeks' pregnant and is in preterm labor has been admitted with cervical dilation of 6 cm. She has received betamethasone, and labor suppression is being attempted. You meet with your medical, respiratory therapy, and nursing associates to discuss using a volume-controlled ventilation strategy for the newborn.

Of the following, the effectiveness of volume-controlled ventilation among very-low-birthweight infants is MOST dependent on:

- A. end-expiratory pressure
- B. exogenous surfactant
- C. pharmacologic paralysis
- D. progressive tidal volume reduction
- E. ventilator device

Incorrect:

Correct Answer: A

The infant in the vignette is likely to be delivered within a few hours and before the maximal effects of antenatal steroids. The need for positive pressure ventilation is anticipated and you are considering use of volume-controlled ventilation to limit volutrauma. As you discuss the use of volume-controlled ventilation in the infant in the vignette, you remind the respiratory care clinicians and nurses that this mode of mechanical ventilation is predicated on: (1) avoiding excessive tidal volume (VT), beginning with the first breaths in the delivery room, and (2) maintaining sufficient minute ventilation and functional residual capacity to support gas exchange.

Early studies on ventilator-associated lung injury because of barotrauma demonstrated that injury (in animals) from high airway pressures can be prevented if overdistention of the lung is restricted. These data led to exploration of the concept of volutrauma, that is, injury to the lung resulting from overdistention rather than from high airway pressures (barotrauma). Mechanical ventilation devices to control inhaled volumes of gas were introduced in the care of adults and children, and applied to neonates. However, early devices were not designed to safely provide the small...
volumes of gas required by newborns. Air leaks and other complications occurred frequently. Pressure controlled ventilation, which was more precisely manageable, became the primary mode of ventilation in neonates in the 1970s. Recent advances in positive pressure ventilation have allowed use of volume or hybrid modes of ventilation even in the tiniest of preterm infants. However, reduction in chronic ventilator-induced lung injury using volume modes of ventilation in preterm infants has yet to be demonstrated.

Early during the introduction of mechanical ventilation in neonates, the importance of end-distending pressure (continuous positive airway pressure, positive end expiratory pressure) to maintain optimal functional residual capacity and minute ventilation and avoid lung injury was demonstrated. Use of lower-than-needed end-distending pressure resulted in inadequate alveolar recruitment and/or alveolar closure on exhalation. Loss of functional residual capacity between ventilated breaths potentiated overdistention of the uncollapsed terminal airways and initiated the cascade of events that led to classic bronchopulmonary dysplasia. Loss of functional residual capacity also contributed significantly to ventilation-perfusion mismatching, intrapulmonary shunting, and need for high peak inspiratory pressures to reopen alveoli on each inspiration. Atelectotrauma is the term used to describe lung injury from positive pressure ventilation starting at lung volumes lower than the functional residual capacity. Thus, for a volume-controlled mode of mechanical ventilation to have maximum benefit, it is essential to maintain functional residual capacity (open lung strategy) with positive end-expiratory pressure.

When administered to very-low-birthweight infants with respiratory distress syndrome, exogenous surfactant has been shown to reduce mortality and air leaks but had no effect on bronchopulmonary dysplasia. The primary physiologic effect of exogenous surfactant is to help establish and maintain functional residual capacity. At optimal lung volume, compliance is also optimized and the amount of mechanical support required to achieve adequate minute ventilation can be minimized. Although surfactant supplementation can help support minute ventilation, some infants born at 25 weeks' gestation respond to a strategy involving the use of nasal continuous airway pressure to establish a functional residual capacity and avoid the need for mechanical ventilation altogether. About 30% of extremely preterm infants with moderate or severe respiratory distress respond quickly to mechanical ventilation with positive end-distending pressure while avoiding the need for exogenous surfactant. Therefore, assisted ventilation using volume-controlled strategies does not specifically depend on exogenous surfactant for success.

Use of volume targeting from the delivery room onward requires attention to the expected changes in Vt after birth. Initial settings of 4 to 5 mL/kg often suffice, with 6 mL/kg suggested for extremely low-birthweight infants to compensate for the dead space contributed by the flow sensor. With time, Vt needs to be increased progressively as the anatomical and physiological dead space volumes increase because of physiologic recruitment of alveoli, clearance of pulmonary fluids, and distention of airways. The effective Vt also may be reduced because of the increasing air leak at the laryngeal and upper tracheal level caused by progressive airway distention associated with positive pressure ventilation and the use of uncuffed endotracheal tubes.

In some preliminary studies comparing modes of ventilation, volume-controlled ventilation with sufficient end-expiratory pressures has been associated with fewer air leaks than is pressure-controlled ventilation. This effect is credited to positive end-distending pressure maintaining alveolar aeration with an open lung strategy, resulting in more even distribution of ventilation.

Paralytic agents occasionally may be used to avoid asynchronous breathing (“fighting the ventilator”), but they are neither necessary nor sufficient to ensure optimal ventilation in any mode. When spontaneous breathing is desired and the process of weaning has begun, problems associated with weak spontaneous efforts and high airway resistance from a narrow endotracheal tube may be ameliorated through the use of assist-control or patient-initiated ventilation.

The debate as to whether hitting the target should be credited to the Indian or to the arrow applies here as well. As better golfers get better scores than the less-experienced, regardless of the clubs they use, success with a given ventilator device relates to the experience with and knowledge of the device being used. The same can be said for the use of various modes of ventilation, be they “conventional” or “high frequency” techniques. Before embarking on a change, it is important that all those treating the patient and handling the device(s) are fully educated.

References:


Related readings from Neoreviews.org


Philip AGS, Delivoria-Papadopoulos M. Historical perspectives: forty years of mechanical ventilation ... then and now... NeoReviews. 2003;4(12):e335-e339. Available at: http://neoreviews.aappublications.org/cgi/content/full/4/12/e335?fulltext [subscription required]. Accessed November 18, 2009

American Board of Pediatrics Content Specification(s):

04_Respiratory: Know the effects and risks of PPV

04_Respiratory: Know the prenatal and postnatal risk factors for bronchopulmonary dysplasia/chronic lung disease and be aware of various preventive strategies

04_Respiratory: Know factors that determine residual lung volume, functional residual capacity, and tidal volume, and how they change with various pulmonary disorders

04_Respiratory: Know the indications for and techniques of continuous positive airway pressure (CPAP)

04_Respiratory: Know the pathogenesis, pathophysiology, and pathologic features of bronchopulmonary dysplasia/chronic lung disease
A 2-week-old female infant, who was born at full term after an uncomplicated pregnancy and spontaneous vertex vaginal delivery to a 28-year-old primiparous woman, is being evaluated for irregular respiration. The infant has prolonged periods of apnea varying in duration from 30 minutes to 6 hours, interspersed with periods of sustained spontaneous respiration. During the period of apnea, the infant shows cyanosis, absent arousal and distress, subnormal body temperature, decreased muscle tone, and normal tendon and pupillary reflexes. An arterial blood gas measurement reveals a pH value of 6.98; partial pressure of carbon dioxide, 108 mm Hg (14.4 kPa); partial pressure of oxygen 46 mm Hg (6.1 kPa); and base deficit 12 mEq/L (12 mmol/L). In contrast, during the period of sustained spontaneous respiration, the infant is pink in room air, is awake and alert, has normal body temperature, shows no neurologic abnormalities, and has normal arterial blood gases.

Physical examination of the infant reveals no congenital anomalies or dysmorphic features. Findings on cranial magnetic resonance imaging, chest radiography, electrocardiography, and echocardiography are normal. Likewise, serum concentrations of various metabolites including glucose, electrolytes, and amino acids are normal. There are no indications of sepsis or meningitis based on clinical history, blood cell counts, inflammatory markers, or cerebrospinal fluid findings.

The infant is supported with assisted positive pressure ventilation and a fraction of inspired oxygen of 0.25. She is sustained with full enteral feeds of human milk by nasogastric gavage and is receiving no medications other than supplemental vitamins. A trial of caffeine treatment failed to improve her respiratory pattern.

Family history of the infant is negative for breathing disorders, gastrointestinal anomalies, other birth defects, or tumors. You obtain a blood sample for molecular genetic testing.

Of the following, the gene MOST likely to be defective in this infant is:

- **A.** brain-derived neurotrophic factor (BDNF)
- **B.** endothelin 3 (EDN3)
- **C.** human achaete-scute homolog 1 (HASH1)
- **D.** pairedlike homeobox 2B (PHOX2B)
- **E.** rearranged during transfection proto-oncogene (RET)

Incorrect: Correct Answer: D
The infant in this vignette has clinical features consistent with the diagnosis of congenital central hypoventilation syndrome (CCHS). CCHS is a rare disorder with an estimated incidence of 1 in 200,000 live births. A failure of automatic control of breathing is the hallmark of CCHS. The clinical diagnosis of CCHS is based typically on the following criteria:

- hypoventilation during sleep (especially quiet or non–rapid-eye-movement sleep)
- absent or blunted ventilatory sensitivity to hypercarbia during sleep
- absent or variable ventilatory sensitivity to hypoxemia during sleep
- absence of arousal and distress during hypoventilation
- adequate ventilation during wakefulness
- absence of primary pulmonary disease, cardiac disorder, neuromuscular dysfunction, or metabolic aberration

Most cases of CCHS manifest during the first year of age, typically in the newborn period. The severity of ventilatory dysfunction may range from mild hypoventilation during sleep but adequate ventilation during wakefulness, to complete apnea during sleep with hypoventilation even during wakefulness. The infant in this vignette may represent a milder variant of the disease.

Infants with CCHS often have anatomic and physiologic manifestations of a generalized autonomic nervous system dysfunction. Approximately 15% to 20% of infants with CCHS have Hirschsprung disease, which is characterized by aganglionosis of the bowel resulting from neural crest migrational abnormalities. The concomitant occurrence of CCHS and Hirschsprung disease is often referred to as Haddad syndrome. Approximately 5% of infants with CCHS have neural crest–derived tumors, such as neuroblastoma and ganglioneuroma. Other manifestations of autonomic dysfunction observed in infants with CCHS include decreased heart rate variability, decreased breath-to-breath variability, pupillary abnormalities, body temperature instability, esophageal dysmotility, and sporadic profuse sweating. The infant in this vignette may represent a nonsyndromic variant of the disease.

Although most cases of CCHS are sporadic in occurrence, as may be the case in this vignette, a strong genetic basis for CCHS has been suggested by several observations. These observations include occurrence of familial cases of CCHS in monozygotic twins, concomitant presence of other genetically determined conditions such as Hirschsprung disease and neural crest tumors, and reports of vertical transmission of CCHS in families. Candidate gene studies exploring specific gene mutations in affected infants and families have suggested that CCHS is an autosomal dominant disorder.

The major disease-causing gene for CCHS is pairedlike homeobox 2B gene (PHOX2B). Human PHOX2B gene is located on chromosome 4p12. It encodes a highly conserved homeobox domain transcription factor of 314 amino acids, with one short region of nine polyalanine repeats and a second longer region of 20 polyalanine repeats. It is this second region that is of primary importance in CCHS. As reported by Berry-Kravis and associates, 92% (185/201) of patients with CCHS are heterozygous for de novo expansion to 25 to 33 polyalanine repeats (compared with normal 20). The remaining 8% (16/201) of patients with CCHS have missense, nonsense, or frameshift mutations at the 3’ end of the PHOX2B gene. Both the polyalanine repeat expansion and nonpolyalanine repeat mutation account for cytoplasmic aggregation of the mutant protein with resultant loss of nuclear transcription function. Testing for PHOX2B polyalanine repeat expansion using a polymerase chain reaction–based assay is available for molecular genetic confirmation of the clinical phenotype of CCHS.

Brain-derived neurotrophic factor (BDNF) is a prosurvival factor induced by cortical neurons and is critical for the survival of cholinergic and motor neurons of the forebrain. Human BDNF gene is located on chromosome 11p13. It encodes a 247–amino acid preproprotein that is proteolytically cleaved into a mature 119–amino acid protein. As reported by Weese-Mayer and associates, only 5% (1/19) of children with CCHS have a mutation of the BDNF gene. This mutation involves a substitution of isoleucine for threonine at the amino acid position 2 in the coding sequence of the BDNF gene. Most single nucleotide polymorphisms involving the BDNF gene are associated with conditions such as episodic memory deficit, obsessive compulsive disorder, anorexia nervosa, bipolar affective disorder, and Parkinson disease.

Endothelin 3 (EDN3) is a vasoactive peptide that exerts a dose-dependent stimulation of proliferation and melanogenesis in neural crest cells. Human EDN3 gene is located on chromosome 20q13.2-q13.3. It encodes a 230–amino acid precursor that yields endothelin.
As reported by Bolk and associates, only 7% (1/14) of children with CCHS have a mutation of the \textit{EDN3} gene. This mutation involves a 1-base pair (bp) insertion of an adenosine in exon 4 of the \textit{EDN3} gene. Most mutations involving the \textit{EDN3} gene are associated with conditions such as isolated Hirschsprung disease and Waardenburg-Shah syndrome (colonic aganglionosis, sensorineural hearing loss, and pigmentary anomalies of the skin and retina).

Human achaete-scute homolog 1 (HASH1) is a transcription factor that regulates the development of mammalian central nervous system and neural crest. Human \textit{HASH1} gene is located on chromosome 12q22-q23. It encodes a 238-amino acid protein that contributes to 65% of neocortical neurons, mostly in the ventricular and subventricular zones of the dorsal forebrain. As reported by de Pontual and associates, only two patients with CCHS have been identified to carry a mutation of the \textit{HASH1} gene. This mutation involved a 15-bp deletion that resulted in a loss of 5 of 13 alanine residues in the polyalanine tract of the \textit{HASH1} gene. Most mutations involving the \textit{HASH1} gene are associated with neuroendocrine tumors.

Rearranged during transfection (RET) proto-oncogene is one of the receptor tyrosine kinases. Human \textit{RET} gene is located on chromosome 10q11.2. It encodes tyrosine kinase receptors, cell surface molecules that transduce signals for cell growth and differentiation. As reported by Amiel and associates, only 14% (1/7) of children with CCHS have a mutation of the \textit{RET} gene. This mutation involves a substitution of leucine for proline in exon 19 of the \textit{RET} gene. Most mutations involving the \textit{RET} gene are associated with conditions such as multiple endocrine neoplasia, Hirschsprung disease, medullary thyroid carcinoma, pheochromocytoma, and renal anomalies.

References:


Related readings from Neoreviews.org


American Board of Pediatrics Content Specification(s):

04_Respiratory: Know the effects of pulmonary reflexes and oxygen, carbon dioxide, and hydrogen ion concentrations on control of neonatal breathing

05_Genetics_Dysmorphism: Know basic functional units of a gene, including intron, exon, promoter, enhancer, and polyadenylation sequence
05_Genetics_Dysmorphism: Know concept of DNA and mRNA sequence encoding amino acid structure of proteins

05_Genetics_Dysmorphism: Recognize clinical features associated with autosomal dominant disorders

05_Genetics_Dysmorphism: Demonstrate understanding of inheritance patterns and recurrence risks for autosomal dominant disorders

05_Genetics_Dysmorphism: Know the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis

11_Gastroenterology: Know the pathological, clinical, and diagnostic features of Hirschsprung disease, including other associated clinical conditions
You are asked to see a 3,200-g, 38 weeks’ gestation infant because of respiratory distress. Her mother’s pregnancy, labor, and delivery were uncomplicated. The infant’s Apgar scores were 7 and 8 at 1 and 5 minutes, but she now has mild grunting respirations and intercostal retractions. She requires 0.30 fraction of inspired oxygen to remain pink. The infant’s mother shares the information that one of her two older children has “stiff lungs just like his father,” but he did not “breathe hard” when he was a baby. No breathing problems are known among her relatives.

Of the following, the lung dysfunction pattern seen in this family is MOST consistent with gene disorders controlling the function of:

- A. ABCA3 transporter
- B. ABCA7 transporter
- C. surfactant protein A
- D. surfactant protein B
- E. surfactant protein C

Correct Answer: E

Term and late-preterm infants presenting with a clinical syndrome of respiratory distress may have one of the genetic conditions that affect surfactant or lung function. If neonatal respiratory distress is not explained by more common conditions such as transient tachypnea, aspiration, pneumonitis, or persistent pulmonary hypertension, the underlying problem may be a hereditary condition. The pattern in the vignette suggests an autosomal dominant inheritance pattern of a condition more likely to be chronic than lethal. Disorders affecting the gene controlling surfactant protein C (SPC) are most consistent with the family in the vignette.

Surfactant protein C plays an important, but not dominant, role in lung homeostasis. SPC is encoded by a single gene (SFTPC) located on chromosome 8, which results in the production of a 191-amino acid proprotein by type II pulmonary epithelial cells. Proteolytic processing within the type II cell results in active SPC. Active SPC is tightly associated with surfactant lipids in airspaces, enhances their spreading, and recruits lipids to surface films. Because surfactant protein B (SPB) is required for the proteolytic...
processing and secretion of SPC, SPC is absent from lung secretions in both SPB and SPC deficiency states. Although SFTPC mutations usually produce no symptoms in the neonate, occasional infants have had clinical patterns as severe as that seen with SPB deficiency. The usual pattern is one of interstitial pneumonitis beginning in infancy or childhood; adults are classified as having idiopathic pulmonary fibrosis, usual or nonspecific interstitial pneumonitis, or desquamating interstitial pneumonitis. A pattern of dominant inheritance of the previously cited conditions supports the diagnosis; definitive diagnosis can be confirmed by identification of mutations in the SFTPC gene. Sporadic de novo mutations have been reported, as would be expected with an autosomal dominant condition. Treatment is symptomatic and some individuals experience an improved quality of life after lung transplantation.

Disorders affecting mutations of the ABCA3 transporter gene have been demonstrated to cause acute respiratory distress in newborns and chronic interstitial lung disease in adults. ABCA3 is a member of the ATP-binding cassette (ABC) transporters. The exact function of ABCA3 in the lung is not known. It is expressed in type II epithelial cells and is suspected to have a role in lipid transport to or from the lamellar bodies. Autosomal recessive conditions frequently cause disease in a sibling or consanguinity may appear in the family history; having an affected parent is rare. The clinical pattern is one of severe, usually fatal, respiratory distress in the newborn period. The condition is unaffected by exogenous surfactant, assisted ventilation, or extracorporeal membrane oxygenation. This finding is not consistent with the family in the vignette.

Another gene in the ABC family, ABCA7, also known as CFTR, is the gene associated with cystic fibrosis. Abnormalities in CFTR are inherited in an autosomal recessive pattern. Respiratory distress in the neonatal period is not often associated with cystic fibrosis; the most common neonatal manifestation is meconium ileus.

The major function of surfactant protein A (SPA) involves innate immunity. In contrast to SPB and SPC, SPA is secreted by nonlamellar body secretory vesicles of the type II respiratory epithelial cell. No genetic syndrome involving SPA has been implicated as a cause of neonatal or adult respiratory disease.

More than 25 distinct abnormalities in the structure of the human SPB gene, SFTPB, have been documented. Inheritance is in an autosomal recessive pattern. Carriers of SFTPB mutations have not been affected by clinical lung disease. Located on chromosome 2, SFTPB controls the production of a 381-amino acid precursor of SPB in type II pulmonary epithelial cells. Active SPB, with 79 amino acids, results from proteolytic processing of the precursor as it progresses through the endoplasmic reticulum, Golgi apparatus, and multivesicular bodies to the lamellar bodies, where the active SPB is stored before it is secreted. In the alveolus, SPB interacts strongly with surfactant phospholipids, creates the monolayers and multilayers of stable surfactant, and causes a reduction in surface tension during breathing. Some mutations affect the synthesis of the mRNA required to synthesize the precursor; other mutations result in an abnormal precursor protein leading to defective synthesis of active SPB. SPB also is required for the normal metabolism of other surfactant proteins. When SPB is absent, SPC is not secreted. Although most affected individuals present with profound surfactant dysfunction resulting in lethal respiratory distress during the neonatal period, case reports have attributed severe chronic lung disease to partial defects in SPB synthesis. This pattern is not consistent with the family in the vignette.

References:


Related material from NeoReviews.org:


Jobe AH. Pharmacology review: why surfactant works for respiratory distress syndrome. *NeoReviews*. 2006;7:e95-e106. Available at: [http://neoreviews.aappublications.org/cgi/content/full/7/2/e95](http://neoreviews.aappublications.org/cgi/content/full/7/2/e95) Accessed May 18, 2010


**American Board of Pediatrics Content Specification(s):**

04_Respiratory: Know the timing of the biochemical maturation of the lung and the physiological and biochemical factors affecting this timing

04_Respiratory: Know the stages and mediators of normal and abnormal cellular and structural development of all components of the lung
November

ASSESSMENT PROGRESS: Total Questions: 10 Questions Answered: 9 Correct Answers: 2

Question 9

A full-term male infant who made a good transition was sent home with his parents 24 hours after birth. He was their third child and the mother's obstetric history was unremarkable. He was seen 2 days after discharge, and his physical examination findings were normal for his age. His transcutaneous bilirubin concentration was 11 mg/dL (188 \( \mu \)mol/L). At 12 days the parents report that his feeding changed from vigorous to weak. He stopped feeding often to catch his breath. Sweat appeared on his forehead and his breathing was labored even between feedings.

The infant was taken to a pediatric emergency service. His vital signs included a temperature of 36.5°C, heart rate of 186 beats per minute, and respiratory rate of 72 breaths per minute. He had chest retractions, and his weight was 5% greater than his birthweight. He had a loud holosystolic murmur most prominent at the left sternal border. Fine rales were heard over the posterior lungs. Chest radiography and Doppler echocardiography were performed (Figures 1 and 2).

Figure 1
Of the following, the MOST abnormal measure of pulmonary function in this infant would be:
A. airway resistance
B. crying vital capacity
C. expiratory reserve volume
D. minute ventilation
E. respiratory system compliance

**Incorrect:**

Correct Answer: E

The infant in the vignette was well from the time of birth until 2 weeks later, when he developed dyspnea, especially with the effort associated with feeding. He was sweating with exertion. Physical examination revealed a new heart murmur and rales. Rales are caused by the popping open of small airways that have been closed with intraluminal fluid. His chest radiograph (Figure 1) shows an enlarged heart and pulmonary congestion/edema, signs consistent with congestive heart failure. The echocardiogram (Figure 3) demonstrates a large left-to-right shunt through a ventricular septal defect.

Figure 3: Echocardiogram showing a large left-to-right shunt coursing through a ventricular septal defect. (Courtesy of Jon Love, MD, University of New Mexico.)

The infant had two early physical examinations that did not detect his congenital heart disease. This happens frequently with large ventricular septal defects. Pulmonary vascular resistance is high in utero and at birth. In the normal infant, pulmonary vascular resistance begins to fall shortly after air breathing is initiated. As the pulmonary resistance falls in the infant with a ventricular septal defect, a left-to-right shunt across the defect starts increasing the blood volume of the pulmonary vascular circuit. This increased volume tends to increase pulmonary arterial pressure and reduce the blood flow across the defect. Eventually the excess pulmonary vascular volume increases intracapillary pressure, facilitates leakage of fluid into airway spaces, and results in pulmonary edema as seen in the chest radiograph.
The main alteration in pulmonary function associated with pulmonary edema is reduction in lung compliance. Compliance is the ratio of change in lung volume divided by change in pressure. When the lungs become more difficult to expand, this ratio becomes smaller (i.e., lower compliance). A fixed change in pressure will produce a smaller volume change in a lung that has excess vascular leakage of fluid than the change in volume that would be seen in a normal lung. A decrease in compliance is manifested clinically by chest wall retractions during inspiration without airway noises such as stridor and wheezing. For infants with pulmonary edema, compliance improves with the administration of diuretics.

Airway resistance is measured by the speed (volume per second) at which air is expelled from the lungs and depends on the diameter of medium to large airways. Increased resistance in these passages results in stridor with narrowing at the level of the larynx or trachea, or in wheezing with the narrowing of smaller airways. Pulmonary edema does not affect the diameter of large and medium-sized airways and does not impede the flow of air through them.

With enough effort (e.g., crying), infants with congestive heart failure can fill their lungs with a similar volume of air per body weight as normal infants. The crying vital capacity is the volume of air expelled from maximum inspiration to maximum expiration while the infant is crying. Vital capacity is composed of two components: the inspiratory capacity (from the end of a normal tidal volume to maximum inspiration) and the expiratory reserve volume (from the end of a normal tidal volume to maximum expiration). Neither the crying vital capacity nor its components is affected by pulmonary edema.

Infants with congestive heart failure often have blood gas measurements in the normal range. The partial pressure of carbon dioxide in their blood depends on normal minute ventilation (breaths per minute multiplied by tidal volume). However, decreased compliance may tend to reduce the average tidal volume. In the case of infants with congestive heart failure, normal minute ventilation is sustained in the face of reduced tidal volumes by increasing the respiratory rate. Tachypnea is reported commonly in infants with congestive heart failure.

References:


Related readings from NeoReviews.org


04_Respiratory: Know the causes of pulmonary edema and its effects on lung function

Continue
A 28-year old pregnant woman presents at full term with excessive vaginal bleeding. An emergency cesarean delivery is performed because of concern for placental abruption. At birth, the male infant has a normal respiratory effort, an elevated heart rate, and pallor. His initial hematocrit is 25%, prompting fluid resuscitation with packed red blood cells. After the transfusion, the neonatologist teaches the pediatric residents about the importance of preload by using a ventricular function curve.

**Figure 1**

Of the following, the additional cardiac measurement that can MOST appropriately be labeled on the x-axis in **Figure 1** is:

- A. afterload
- B. cardiac output
- C. diastolic cardiac muscle length
- D. inotropy
- E. stroke work

**Incorrect:**
Correct Answer: C
The ventricular function curve in Figure 1 illustrates the Frank-Starling principle. This principle states that increased diastolic filling of the left ventricle (LV) produces greater stretch of the cardiac muscle, resulting in a larger stroke volume. Thus, if there is greater filling during diastole, the LV will contract more forcefully during systole to eject this extra blood volume. Two mechanisms can explain this occurrence:

- with an increase in preload, there is more optimal overlap between the thin and thick muscle filaments
- as cardiac muscle is stretched, troponin C is more sensitive to calcium

The Frank-Starling principle is shown graphically in Figure 2: an increase in the LV end-diastolic volume from point X to point Y creates a greater force of ventricular contraction and thus a larger stroke volume.

Figure 2: This ventricular function curve demonstrates that the increased diastolic filling of the left ventricle (LV) produces greater stretch of the cardiac muscle, resulting in a larger stroke volume. An increase in the LV end-diastolic volume from point X to point Y creates a greater force of ventricular contraction and thus, a larger stroke volume.

The label of the x-axis in the ventricular function curve corresponds with the preload of the LV. Preload can be represented by the LV end-diastolic volume, as shown in Figure 1. If ventricular end-diastolic volume increases, the ventricular fiber length also increases, leading to an increased muscular tension; thus the x-axis of the graph in this vignette also can be labeled as diastolic cardiac muscle length (Figure 3). Both the degree of end-diastolic fiber stretch and end-diastolic volume are influenced by ventricular diastolic pressure. Thus, the LV end-diastolic pressure, especially if it is above normal, typically measures the preload of the LV and also can be designated on the x-axis of the ventricular function curve (Figure 3).

Figure 3: This figure demonstrates all the possible cardiac measurements that can be used to graph the ventricular function curve. While the x-axis corresponds to the preload of the LV and can be represented as LV end-diastolic volume, diastolic cardiac muscle length, or LV end-diastolic pressure, the y-axis designates the heart’s pumping ability and can be labeled as stroke volume, cardiac output, LV systolic pressure, or stroke work.
Changes in afterload do not correspond to the x- or y-axis of the ventricular function curve but rather, shift the curve itself (Figure 4). If there is an increase in afterload, stroke volume decreases, leading to an increase in end-systolic volume. This extra volume is added to the venous return to the LV, which increases LV end-diastolic volume as well. Thus, an increase in afterload shifts the Frank-Starling curve down and to the right (from point X to point B). A decrease in afterload shifts the ventricular function curve up and to the left (from point X to point A).

**Figure 4:** This figure shows the effect of changes in afterload on the ventricular function curve. An increase in afterload shifts the Frank-Starling curve down and to the right (from point X to point B) and a decrease in afterload shifts the ventricular function curve up and to the left (from point X to point A).

While the x-axis of the ventricular function curve corresponds with the LV’s preload, the y-axis represents the pumping ability of the LV. Because stroke volume is directly related to cardiac output (cardiac output = stroke volume × heart rate), cardiac output may be represented on the y-axis of the ventricular function curve (Figure 3).

Similar to afterload, inotropy does not correspond to the labeling of the x- or y-axis of the ventricular function curve but rather, is represented by changes in the slope of the curve (Figure 5). If ventricular contractility increases, the ventricular function curves shifts upward and to the left; thus, stroke volume (point A) is higher for a given end-diastolic volume (point X). This upward shift may indicate use of an inotropic agent. In contrast, decreased contractility leads to a downward shift in the ventricular function curve, yielding a lower stroke volume (point B) for a given end-diastolic volume (point X), as observed in patients with congestive heart failure.
Figure 5: This figure shows the changes in the ventricular function curves as inotropy is altered. If ventricular contractility increases, the ventricular function curves shift upward and to the left; thus, the stroke volume (point A) is higher for a given end-diastolic volume (point X). In contrast, decreased contractility leads to a downward shift in the ventricular function curve, yielding a lower stroke volume (point B) for a given end-diastolic volume (point X).

Stroke volume

Increased contractility

Normal

Congestive heart failure

Left ventricular end-diastolic volume

Stroke work is directly related to stroke volume (stroke work = mean arterial blood pressure \times stroke volume). Thus, stroke work can also be designated on the y-axis of the ventricular function curve to denote the heart’s pumping ability (Figure 3).

References:


Related articles from NeoReviews.org


American Board of Pediatrics Content Specification(s):

03. Cardiovascular: Know the factors affecting and regulating myocardial performance and function in the fetus and newborn infant and during the transitional period
You are consulting with a woman and her family about stabilization procedures and outcomes for infants born between 24 and 27 weeks’ gestation. The woman is now 25 weeks pregnant and is in preterm labor despite tocolysis. The pregnancy has otherwise been uncomplicated. Maternal betamethasone dosing was completed 24 hours previously. The father asks whether there is any short-term advantage or risks to initial stabilization with continuous positive airway pressure (CPAP) compared with intubation and prophylactic surfactant administration.

Of the following, the MOST likely short-term outcome that is improved by initial stabilization of the infant with CPAP is:

A. air leak
B. bronchopulmonary dysplasia or death
C. endotracheal intubation
D. intraventricular hemorrhage
E. severe retinopathy of prematurity

An optimum strategy for resuscitation of infants born before 28 weeks of gestation has not been determined. The surfactant trials performed in the 1980s and early 1990s showed an advantage to initial resuscitation with intubation and surfactant administration. Survival was improved, fewer air leaks occurred, and severity of respiratory distress was reduced. The incidence of bronchopulmonary dysplasia in infants of lower gestational age was not changed with prophylactic surfactant administration. A prophylactic surfactant strategy also had the disadvantage of treating infants who had mild or no respiratory distress syndrome (about 30% of infants born <30 weeks’ gestation). Furthermore, antenatal corticosteroid administration was shown to improve survival and other outcomes in very preterm infants (with the exception of bronchopulmonary dysplasia). Administration of corticosteroids to women in preterm labor was infrequent during the early surfactant trials.

Subsequent to the early surfactant trials, antenatal corticosteroid use has increased dramatically. More than 80% of eligible women are treated today. A number of observational studies have also implicated initial positive pressure ventilation and mechanical ventilation in the pathogenesis of the alveolar arrest and lung injury that characterizes bronchopulmonary dysplasia. Among women who received antenatal corticosteroids, a delivery room strategy using continuous positive airway pressure (CPAP) was compared with a prophylactic surfactant strategy in infants born at less than 28 weeks’ gestation. Short-term outcomes of this landmark study from the SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network were published in May 2010; neurodevelopmental outcomes measured in the latter half of the second year after birth in the Network study and similar studies performed by other networks are yet to be reported (as of October 2010).
Extremely preterm infants treated with a CPAP strategy in the delivery room required endotracheal intubation less frequently than those who were treated with the prophylactic surfactant strategy. In the delivery room, 34% of the CPAP group received endotracheal intubation for any reason (apnea, severe respiratory failure) compared with the prophylactic surfactant group (93%). During the hospitalization, however, 83% of extremely preterm infants received endotracheal intubation for any reason. In the delivery room, 33% of the CPAP group and 27% of the surfactant group required endotracheal intubation for resuscitation purposes, not for surfactant administration. The implications are that about 30% of extremely preterm infants will need endotracheal intubation in the delivery room and all but approximately 17% will receive endotracheal intubation at some time during their birth hospitalization.

The primary outcome—death or bronchopulmonary dysplasia—at 36 weeks’ gestation was not different between the study groups (CPAP 48% vs. surfactant 51%; relative risk = 0.95; 95% confidence interval = 0.85-1.05). The CPAP group required fewer days of mechanical ventilation (CPAP 25 days vs. surfactant 28 days; P=.03), had a better survival rate without mechanical ventilation at 7 days of age (CPAP 55% vs. surfactant 49%; P=.01), and had a lower rate of postnatal corticosteroid use (CPAP 7% vs. surfactant 13%; P < .001). The implication from these short-term outcomes is that a CPAP delivery room stabilization strategy and a strategy using intubation with prophylactic surfactant both are similarly effective for resuscitating infants born before 28 weeks’ gestation. The CPAP strategy is not associated with a higher incidence of acute complications (such as severe retinopathy of prematurity, bronchopulmonary dysplasia, air leaks, necrotizing enterocolitis, and intraventricular hemorrhage) and may have some short-term advantages (incidence of endotracheal intubation, survival without mechanical ventilation at 7 days of age, days of mechanical ventilation).

Subsequent reports about longer-term and neurodevelopmental outcomes and similarly designed studies in other research networks will contribute additional important information about the benefits and risks of different delivery room resuscitation strategies for extremely preterm infants.

References


Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2001;2:CD000510


American Board of Pediatrics Content Specification(s)

Respiratory: Know the clinical strategies and therapies used to decrease the risk and severity of RDS

Respiratory: Know the management of RDS, including surfactant replacement

Asphyxia and Resuscitation: Know the proper approach to airway management in the delivery room

Asphyxia and Resuscitation: Know the potential complications of airway management in the delivery room and know their management

Asphyxia and Resuscitation: Know the indications for assisted ventilation immediately after birth and how to assess its effectiveness
Question: 2

During a routine pediatric visit at 2 months of age, a female infant was noted to have poor weight gain and tachypnea with increased work of breathing. Her respiratory symptoms progressed and by the end of the week, she required admission to the hospital and mechanical ventilation. She was dependent on the ventilator for a prolonged period but then recovered and was discharged from the hospital at 5 months of age.

Two years later, the parents of this infant had a second female child who did not have any lung disease. However, their third child presented immediately after birth with severe hypoxemic respiratory failure from which he did not survive despite maximal therapy. Testing revealed that this infant had a similar protein deficiency as their first child, which was not present in their middle child or either parent.

Of the following, the MOST likely protein that is deficient in the two symptomatic siblings is:

- A. ATP-binding cassette member A3
- B. surfactant protein A
- C. surfactant protein B
- D. surfactant protein C
- E. surfactant protein D

Surfactant deficiency may be attributable to decreased production because of pulmonary immaturity or as a result of genetic mechanisms that disrupt the production of critical proteins involved in surfactant function and metabolism. Although inherited surfactant deficiency disorders are rare, their associated morbidities and mortalities are high. At present, the most commonly known surfactant disorders result from deficiencies in the surfactant lipid-associated transporter known as adenosine triphosphate (ATP)-binding cassette member A3 (ABCA3), surfactant protein (SP)-B, or SP-C (Table). Disorders associated with these protein deficiencies have different inheritance patterns, variable onset and severity of clinical disease, and distinct pathogeneses.

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Genetics</th>
<th>Onset of Clinical Symptoms</th>
<th>Radiographic Similarity to RDS vs ILD</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCA3</td>
<td>Autosomal recessive</td>
<td>Neonatal period most common</td>
<td>RDS or ILD</td>
<td>Variable (typically lethal without transplant if presents in neonatal period)</td>
</tr>
<tr>
<td>SP-B</td>
<td>Autosomal</td>
<td>Neonatal period</td>
<td>RDS</td>
<td>Fatal without</td>
</tr>
</tbody>
</table>

Table: Comparison of Inherited Surfactant Deficiency Disorders
Abnormal surfactant production leads to respiratory distress syndrome (RDS) and is usually the result of deficiencies in one of the surfactant proteins. The severity of RDS ranges from mild to life-threatening, and factors other than genetic causes can affect the degree of lung disease. The clinical course of RDS can vary based on the underlying genetic cause.

**Surfactant Protein C Deficiency (SP-C)**

SP-C deficiency is an autosomal recessive disorder. Deficiency of SP-C results in a more severe form of RDS due to reduced surfactant production and function. The clinical presentation of infants with SP-C deficiency is characterized by signs and symptoms of severe respiratory distress, often requiring immediate medical intervention such as ventilator support and surfactant administration. The severity of lung disease can vary, with some infants dying within the first few hours of life.

**Surfactant Protein B Deficiency (SP-B)**

SP-B deficiency is an autosomal recessive disorder and is the most common known genetic cause of RDS. Infants with SP-B deficiency typically present with respiratory distress within the first few hours of life and require immediate mechanical ventilation. The severity of lung disease can range from mild to severe, with some infants requiring long-term mechanical ventilation and others needing extracorporeal membrane oxygenation (ECMO).

**Adenosine Triphosphate-Binding Cassette Member 3 (ABCA3) Deficiency**

ABCA3 deficiency is an autosomal recessive disorder and is the most common known genetic cause of RDS. Infants with ABCA3 deficiency typically present with respiratory distress within the first few hours of life and require immediate mechanical ventilation. The severity of lung disease can range from mild to severe, with some infants requiring long-term mechanical ventilation and others needing extracorporeal membrane oxygenation (ECMO).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Type</th>
<th>Onset</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP-C deficiency</td>
<td>Autosomal</td>
<td>Infancy</td>
<td>Neonatal period less common</td>
</tr>
<tr>
<td></td>
<td>recessive</td>
<td>Adulthood</td>
<td>ILD more common than RDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Variable</td>
</tr>
</tbody>
</table>

**Summary:**

Deficiency of ABCA3 is an autosomal recessive disorder and is the most common known genetic cause of surfactant deficiency. The clinical course can vary, with term infants presenting immediately after birth with respiratory distress syndrome and/or pulmonary hypertension. A subgroup of these infants may progress rapidly to hypoxic respiratory failure and death despite maximal medical therapy. Other infants may gradually improve with persistent mild respiratory symptoms, and be discharged from the hospital. Still other infants may appear healthy in the neonatal period and present later with nonspecific findings such as failure to thrive, digital clubbing, and respiratory signs and symptoms consistent with interstitial lung disease.

The precise role of ABCA3 in surfactant metabolism is not completely understood. Infants deficient in ABCA3 lack desaturated phosphatidylcholine and phosphatidylglycerol, have reduced surface tension–lowering ability, and possess few normal lamellar bodies. These findings suggest that ABCA3 is involved in lamellar body formation and surfactant function. The most likely protein that is deficient in the siblings in the vignette is ABCA3 because of the variability in clinical disease and timing of presentation, as well as an autosomal recessive pattern of inheritance.

At present, there are no known inherited mutations in the genes encoding SP-A. Genetically engineered SP-A–deficient mice do not develop any lung disease. However, these mice are more susceptible to bacterial and viral pathogens in the lung. This latter finding is not surprising given the role of SP-A in providing an innate host defense system to the lungs.

Surfactant protein B deficiency is an extremely rare autosomal recessive disorder with initial clinical manifestations similar to those of ABCA3 deficiency. Neonates with a complete deficiency of SP-B typically are born at full term and present with respiratory distress within a few hours. At presentation, the severity of symptoms and degree of lung disease is variable, with some infants having mild symptoms in the first few postnatal days, and others exhibiting a rapid onset of severe hypoxemic respiratory failure requiring extracorporeal membrane oxygenation. Radiographic findings in all neonates correlate with surfactant deficiency observed in preterm infants.

Regardless of the initial clinical presentation and in contrast to infants with ABCA3 deficiency, all infants with SP-B deficiency have progressive disease, with transient improvement after surfactant administration and modest improvement with corticosteroid therapy. Infants typically die of respiratory failure within 3 to 6 months despite maximal medical therapy; at present, lung transplantation is the only effective therapeutic option. Although the third infant in the vignette had a clinical presentation and onset that could be consistent with SP-B deficiency, the initial onset of disease at 2 months of age with complete recovery in the first child is not consistent with a deficiency of SP-B.

Experiments in genetically engineered mice suggest that a critical level of SP-B expression is required for proper lung function. Indeed, some infants with partial deficiency of SP-B can survive beyond the neonatal period. However, in the presence of additional factors attenuating SP-B production, such as prematurity or inflammation, even infants with partial SP-B deficiency are at high risk of severe lung disease.

In addition to lacking SP-B protein with resultant inability to lower alveolar surface tension, infants with SP-B deficiency lack normal lamellar bodies, and instead have disorganized lamellated vesicular inclusions. This lack of normal lamellar body formation leads to altered phospholipid composition of surfactant with decreased amounts of phosphatidylcholine and phosphatidylglycerol. In addition, this lamellar abnormality may also contribute to the incomplete processing of the SP-C protein to the mature form. This lack of mature SP-C compounds creates a double effect, perhaps contributing to the lethality of SP-B deficiency in the immediate neonatal period.

In contrast to infants with SP-B or ABCA3 deficiency, infants affected by SP-C deficiency typically present after the neonatal period with an acute form presenting during infancy and a chronic form evident during adulthood. The severity of lung disease associated with SP-C gene mutations is highly variable, even among family members with the same genetic abnormality; this suggests that environmental and other genetic factors alter the pathogenesis of this disease. A radiographic pattern of interstitial lung disease is more common than RDS. Unlike SP-B or ABCA3 deficiency, infants with SP-C deficiency can have a mutation on only one allele and this is typically inherited in an autosomal dominant pattern with some sporadic cases being reported. SP-C gene mutations lead to irregular folding of the precursor of SP-C, which is directly toxic to alveolar epithelial cells. Because SP-B protein is unaffected in SP-C–deficient infants, one explanation for the lack of perinatal disease in this group is that SP-B production can compensate for the absence of SP-C. The affected infants in the vignette are unlikely to have a deficiency of SP-C because neither parent is affected and the genetic pattern does not suggest an autosomal dominant inheritance.
Similar to SP-A–deficient mice, mice genetically engineered to lack SP-D expression do not have any perinatal disease. However, SP-D–deficient mice do develop lipid accumulation and emphysema with time. Although an inherited SP-D deficiency has not been identified in humans, infants with this deficiency would probably not present clinically in the neonatal period.

**References**


**American Board of Pediatrics Content Specification(s)**

Respiratory: Know the pathophysiology and risk factors for RDS

Respiratory: Recognize the pathologic features of RDS
August

Question View: All (10)

Page 4 of 11

Mode: Learner [ ] Exam

ASSESSMENT PROGRESS: Total Questions: 10 Questions Answered: 10 Correct Answers: 8

Question: 4

A 3-day-old male infant born at 32 weeks’ gestation after 12 weeks of ruptured membranes develops a right tension pneumothorax (Figure 1) while being treated with high-frequency oscillatory ventilation. With the help of a veteran charge nurse you place a chest tube using a Seldinger technique. After you connect the tube to 15 cm of suction, blood begins to completely fill the tubing, and bloody secretions begin to bubble up the endotracheal tube. The nurse comments that this cannot be good because she has never seen it in her 25 years’ experience. After you order a packed red blood cell transfusion and review the infant’s chest radiograph (Figure 2) you discuss the most appropriate next step to control the infant’s hemorrhage with the nursing staff.

Figure 1

Figure 2
Of the following, the treatment MOST likely required to control the hemorrhage is a:

- **A.** chest tube replacement  
- **B.** fresh frozen plasma infusion  
- **C.** ligation of an intercostal artery  
- **D.** pericardiocentesis  
- **E.** thoracotomy

**Correct**

Pneumothorax is defined by the presence of air between the visceral and parietal pleura. Air leaks begin with the rupture of overdistended alveoli. Gas can dissect along the perivascular sheath toward the hilum, resulting in a pneumomediastinum, or toward the pleural space yielding a pneumothorax. As air enters the pleural space and the intrapleural pressure becomes greater than the intrapulmonary pressures, the lung may partially or completely collapse. A tension pneumothorax occurs when air entering the pleural space cannot exit during exhalation (Figure 1). Pneumothoraces occurred in approximately 5% of very-low-birthweight neonates in the Vermont Oxford Network.

As a tension pneumothorax develops:

- \( P_{aO_2} \) decreases
- heart rate and central venous pressure increase
- arterial blood pressure and pulse pressure decrease
- cerebral oxygen delivery decreases

Because of their significant effect on neonatal hemodynamics, tension pneumothoraces, such as experienced by the neonate in the vignette, require immediate attention.
Needle thoracentesis is a rapid means of promptly evacuating pleural air. However, needle thoracentesis often is not sufficient to control the continuous accumulation of air in the pleural space of a neonate receiving mechanical ventilation. Such infants usually will require a chest tube placed in the anterior pleural space connected to 10 to 15 cm of continuous suction pressure. Complications of chest tube insertion can include:

- bruising of the diaphragm or mediastinum
- phrenic nerve injury
- traumatic arteriovenous fistula of the chest wall and lung
- aortic obstruction by a malpositioned tube
- perforation of the lung
- cardiac perforation or tamponade
- hepatic perforation
- hemorrhage

The infant in the vignette has developed a pulmonary hemorrhage following perforation of the lung. Perforation of the lung is probably one of the most common severe complications associated with chest tube placement. In at least one series of neonatal autopsies the incidence was 25%. The lung may become perforated when the tension pneumothorax is relieved and the lung re-expands around a deeply placed needle during a modified Seldinger technique (Figure 3A-E) or the tip of the trocar during a trocar-aided chest tube insertion. As the chest tube is inserted over the wire or trocar, it can lacerate small airways and pulmonary blood vessels resulting in significant hemorrhage through the tube when the chest tube is connected to suction. Although the chest tube was unobstructed, as indicated by the blood coursing through the tubing, the neonate’s ruptured lung had not re-expanded (Figure 2). Placing a new chest tube into the pleural space will serve two functions. It will:

- re-expand the lung so that the bleeding-lacerated vessels can be compressed by inflated alveoli
- drain any ongoing bleeding from the lacerated lung vessels after the original tube is removed

An exploratory thoracotomy would not be indicated as the initial management of the hemorrhage, but may be necessary if the infant remains hemodynamically unstable or if excessive bleeding continues after chest tube reinsertion.

Although blood components such as fresh frozen plasma may be required if excessive whole blood loss is replaced exclusively with packed red blood cells, transfusion of either red blood cells or fresh frozen plasma would not be indicated as initial treatment for a punctured lung with a hemorrhage and a persistent pneumothorax.

During chest tube insertion, intercostal blood vessels, which run beneath each rib, can be lacerated. The intercostal artery and vein can be avoided by ensuring that the chest tube is inserted over the superior surface of the rib. Intercostal vessel laceration is likely to present as bleeding around the chest tube at the insertion site or as a hemothorax.

Pericardial effusions in neonates can be caused by trauma, infectious diseases, inborn errors of metabolism, neoplastic diseases, sequelae of cardiac surgery, congenital diseases, and anticoagulation therapy. Trauma to the pericardium from a deeply placed chest tube can cause a hemorrhagic pericardial effusion. An enlarging cardiac silhouette and a globular heart with a widened base are radiographic findings compatible with a pericardial effusion. The infant's radiographic findings were not consistent with a pericardial effusion (Figure 1, 2) and hemorrhage into the chest tube continued even though the tube was not in contact with the pericardium. A pericardiocentesis would not be indicated.
**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

Respiratory: Know the effects and risks of high-frequency ventilation

Respiratory: Know the indications for and techniques of positive-pressure ventilation (PPV)

Respiratory: Know the effects and risks of PPV

Respiratory: Know the pathophysiology of air leaks

Respiratory: Recognize the clinical, laboratory, and imaging features of air leaks

Respiratory: Know how to prevent and manage air leaks

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September

Question View: All (10)

Page 1 of 11

Mode: Learner [ ] Exam

**ASSESSMENT PROGRESS:** Total Questions: 10  Questions Answered: 10  Correct Answers: 9

**Question: 1**

In preparation for their rotations in the nursery and for delivery room responsibilities, residents, nursing staff, and attending staff members receive education about neonatal resuscitation guidelines and participate in simulation exercises. As you review the *Textbook of Newborn Resuscitation* (6th edition) [2011], some modifications are noted. You plan to emphasize these changes and incorporate them into simulation exercises.

Of the following, the 2011 modified resuscitation guideline MOSTLY emphasizes:

- **A.** avoidance of supplemental oxygen
- **B.** delay in cord clamping
- **C.** earlier use of chest compressions
- **D.** enhanced efforts to avoid hypothermia (Correct)
- **E.** increase in ratio of breaths to compressions

---

**Correct**

The International Liaison Committee on Resuscitation (ILCOR) periodically reviews scientific evidence relevant to resuscitation for use in adults and children, including neonates. Conclusions are published as ILCOR's *Consensus on Science and Treatment Recommendations*, which then are used to formulate the recommendations published in the *American Academy of Pediatrics/American Heart Association Guidelines for Emergency Cardiovascular Care (ECC).* Part of the ECC contains
updates for neonatal resuscitation, which have been incorporated into the *Textbook of Neonatal Resuscitation* (6th edition, 2011). The basic algorithm is presented in Figure 1.

Anticipation and planning for the most appropriate environment and equipment is an important preparatory step for neonatal resuscitation. When newborn resuscitation is imminent, the 2011 recommendations emphasize efforts to avoid hypothermia. Because very-low-birthweight (<1,500 g) preterm infants are at greater risk for hypothermia despite the use of traditional techniques for decreasing heat loss, additional warming techniques are recommended (eg, prewarming the delivery room to 26°C, covering the infant in plastic wrapping (food or medical grade, heat-resistant plastic) (class I, level of evidence [LOE] A), placing the infant on an exothermic mattress (class IIb, LOE B), and placing the infant under radiant heat (class IIb, LOE C). Conductive heat loss can be reduced by prewarming surfaces and materials that will come in contact with the infant. Although head and body cooling have been shown to be helpful in the care of moderately to severely asphyxiated infants, shifting to a body cooling strategy is not recommended as a delivery room environmental strategy. Hyperthermia should be avoided.

Although the new guidelines place less emphasis on the use of oxygen, they do not suggest its avoidance. The current guidelines suggest that use of supplemental oxygen be guided by the pattern of preductal oxygen saturation experienced in the normal birth process, which is added to the algorithm (Figure 2) and is represented in Figure 3.

For full-term infants, resuscitation may be initiated with room air. For preterm infants, a blended air/oxygen mixture is suggested, which thereafter is titrated according to the infant’s oxygen saturation. Thus, supplemental oxygen itself is not to be avoided, it is the unrestricted use of 100% oxygen that is to be avoided.

Oxygen saturation is best evaluated by the use of a pulse oximeter. Pulse oximetry is recommended for high-risk delivery settings and it can be useful any time oxygen is administered. Probes should be applied to the right upper extremity and respond more quickly when placed on the infant before plugging into the monitor. Heart rate can be followed with the pulse oximeter once it is in place, but asystole should be assessed clinically because of possible loss of signal.

Although the infant continues to receive blood from the placenta for a period after delivery and delay in cord clamping for the uncompromised infant is associated with less anemia and better blood pressure, depressed infants have not been shown to benefit from delayed cord clamping. Therefore, the guidelines do not support such a delay when resuscitation is anticipated.

Because of the importance of establishing effective ventilation during neonatal resuscitation, the new algorithm increases a focus on ventilation. When the heart rate is more than 60 beats per minute (bpm) but fails to increase to more than 100 bpm with positive pressure breathing, the first steps are to reconfirm airway patency, reassess the efficacy of assisted breathing, and evaluate oxygen administration. In contrast to resuscitation for acute cardiac events in adults, in which cardiac compressions are of primary importance and assisted breathing is no longer mandated, newborn resuscitation continues to emphasize the need for assisted breathing. When effective ventilation is ensured and the heart rate is less than 60 bpm, addition of external cardiac massage in a ratio of three compressions to one breath should follow. This ratio is similar to that in previous recommendations. Many experts allow for use of 100% oxygen when chest compressions are being performed.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

Asphyxia and Resuscitation: Know the indications for assisted ventilation immediately after birth and how to assess its effectiveness

Asphyxia and Resuscitation: Know indications for and proper administration of supplemental oxygen in the delivery room

Asphyxia and Resuscitation: Know the indications for, techniques, and potential complications of chest compression in the delivery room

Endocrine/Metabolic/Thermal: Know the various types and mechanisms of action of devices to maintain a neutral thermal environment

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Figure 1: Newborn resuscitation algorithm 2010. (Reprinted with permission from Perlman and associates. *Pediatrics*. 2010;126:e1319-e1344.)
Septem

ASSESSMENT 60 sec

Questio

In preparation for newborn resuscitation, the Newborn Resuscitation Program emphasizes:

Of the following interventions, which is correct?

- A. manual ventilation
- B. de-epinephrine
- C. esophageal intubation
- D. enoximone
- E. incision

The International Liaison Committee on Resuscitation (ILCOR) periodically reviews scientific evidence relevant to resuscitation for use in adults and children, including neonates. Conclusions are published as ILCOR’s Consensus on Science and Treatment Recommendations, which then are used to formulate the recommendations published in the American Academy of Pediatrics/American Heart Association Guidelines for Emergency Cardiovascular Care (ECC). Part of the ECC contains updates for neonatal resuscitation, which have been incorporated into the Textbook of

2011.neoreviewsplus.courses.aap.org/script/september#
Figure 2: Newborn resuscitation algorithm (from Kattwinkel and colleagues. *Pediatrics* 2010;126:e1400-e1413).

- **Term gestation? Breathing or crying? Good tone?**
  - Yes, stay with mother
  - No
    - Warm, clear airway if necessary, dry, stimulate
      - No
      - HR below 100, gasping, or apnea?
        - Yes
          - PPV, SpO₂ monitoring
          - No
          - HR below 100?
            - Yes
              - Take ventilation corrective steps
              - No
              - HR below 60?
                - Yes
                  - Consider intubation
                    - Chest compressions
                      - Coordinate with PPV
                        - No
                        - HR below 60?
                          - Yes
                            - IV epinephrine
                            - No
                            - Take ventilation corrective steps
                              - Intubate if no chest rise!
                              - Consider:
                                - Hypovolemia
                                - Pneumothorax
                        - No
                        - Postresuscitation care
                          - Clear airway SpO₂ monitoring
                            - Consider CPAP
                            - Labored breathing or persistent cyanosis?
                              - Yes
                              - Routine care
                                - Provide warmth
                                - Clear airway if necessary
                                - Dry
                                - Ongoing evaluation
                              - No
                              - Targeted Preductal SpO₂ After Birth
                                - 1 min 60%-65%
                                - 2 min 65%-70%
                                - 3 min 70%-75%
                                - 4 min 75%-80%
                                - 5 min 80%-85%
                                - 10 min 85%-90%
      - No
        - HR below 100?
          - Yes
            - Take ventilation corrective steps
            - No
          - HR below 60?
            - Yes
              - IV epinephrine
            - No

Question: 2

A male infant is delivered at 25 weeks’ gestation by a primigravida mother after spontaneous onset of preterm labor. The mother received antenatal betamethasone treatment 48 hours before delivery. Following a vaginal delivery, the infant is spontaneously breathing. His Apgar scores are 7 and 8 at 1 and 5 minutes, respectively. The infant is given 7 cm H₂O nasal continuous positive airway pressure (CPAP) in the delivery room. Two hours after birth, the infant’s work of breathing is labored and the fraction of inspired oxygen has been increased to 0.44 to keep the oxygen saturation between 91% and 95%. Exogenous surfactant is administered.

Of the following, an alternative delivery room resuscitation strategy with SIMILAR short-term outcomes is:

- A. bilevel CPAP and early rescue surfactant
- B. bubble CPAP and early rescue surfactant
- C. endotracheal intubation, late rescue surfactant, and continued mechanical ventilation
- D. endotracheal intubation, prophylactic surfactant, and rapid extubation to CPAP
- E. high flow nasal cannula oxygen and early rescue surfactant

Correct

The mainstays of the perinatal approach to respiratory distress syndrome (antenatal maternal corticosteroids and exogenously administered neonatal surfactant) in preterm infants born at 25 to 28 weeks’ gestation were established during the late 1980s to early 1990s. Antenatal corticosteroids were shown in randomized, controlled trials to decrease mortality, severity of respiratory distress syndrome, use of surfactant, and intraventricular hemorrhage in infants born at less than 30 weeks’ gestation. Exogenous surfactant administered to preterm infants not exposed to antenatal corticosteroids also improved outcomes such as survival, air
leaks (pneumothorax and pulmonary interstitial emphysema), and the combined outcome of death or bronchopulmonary dysplasia. Furthermore, randomized trials of exogenous surfactant in preterm infants not exposed to antenatal corticosteroids established the benefit of administration of prophylactic or early rescue surfactant (within 0.5 to 2 hours of birth) compared with late rescue surfactant (after 2 to 4 hours of birth). Retrospective analysis of randomized trials of exogenous surfactant and a large clinical experience also have suggested that antenatal corticosteroids and exogenous surfactant have additive effects on outcomes of preterm infants.

During the 1990s to early 2000s, large clinical experiences with nasal continuous positive airway pressure (CPAP) in the delivery room, especially after fetal exposure to antenatal corticosteroids, suggested that a strategy of early delivery room nasal CPAP may have outcome advantages over other strategies such as endotracheal intubation and mechanical ventilation or endotracheal intubation, surfactant administration, and ongoing mechanical ventilation. Furthermore, an alternative strategy that combines the potential advantages of prophylactic surfactant and nasal CPAP (endotracheal intubation, prophylactic surfactant, rapid extubation to nasal CPAP, or INSURE) also has been proposed to have outcome advantages over a strategy of using nasal CPAP with early selective surfactant administration.

The infant in the vignette was treated in the delivery room with CPAP followed by early selective surfactant administration. In 2010, Sandri et al reported results of a randomized, controlled, multicenter trial comparing nasal CPAP and early selective exogenous surfactant (treatment strategy for patient in the vignette) with the INSURE strategy. A total of 208 infants born at 25 to 28 weeks’ gestation who were spontaneously breathing after initial resuscitation were randomized; antenatal corticosteroids were given to more than 95% of mothers. The primary outcome of need for mechanical ventilation within 5 days of birth was similar between the groups (31.4% in INSURE group vs. 33% in the nasal CPAP group). Secondary outcomes were also similar during the birth hospitalization, including survival and supplemental oxygen at 36 weeks’ postmenstrual age, air leaks, grade 3 to 4 intraventricular hemorrhage, periventricular leukomalacia, patent ductus arteriosus, retinopathy of prematurity, necrotizing enterocolitis, and moderate to severe bronchopulmonary dysplasia. Thus, delivery room nasal CPAP in breathing infants with selective surfactant administration was equally efficacious as the INSURE strategy which requires endotracheal intubation in the delivery room. In the nasal CPAP group, only 50 (48.5%) infants received exogenous surfactant during their hospitalization. A nasal CPAP strategy has the advantage of intubating and selectively administering surfactant to only half of the infants. Of interest, 42.9% of infants born at 25 to 26 weeks’ gestation and 27.6% of infants born at 27 to 28 weeks’ gestation received mechanical ventilation within 5 days of birth.

Comparative randomized, controlled trials of nasal CPAP with either endotracheal intubation at birth or endotracheal intubation at birth and prophylactic surfactant have not shown differences in primary outcomes. However, secondary outcome differences were noted. In one CPAP versus endotracheal intubation trial, 610 infants born at 25 to 28 weeks’ gestation who had increased work of breathing were randomized to nasal CPAP or endotracheal intubation/mechanical ventilation; surfactant administration was not controlled. Ninety-four percent of mothers received antenatal corticosteroids. The primary outcome, rate of death or bronchopulmonary dysplasia, was 33.9% in the nasal CPAP group and 38.9% in the endotracheal intubation/mechanical ventilation group (odds ratio 0.80, 95% confidence interval 0.58-1.12). The use of surfactant in the nasal CPAP group was half that in the endotracheal intubation/mechanical ventilation group and the incidence of pneumothorax was 9% in the nasal CPAP group compared with 3% in the endotracheal intubation/mechanical ventilation group (P<.001).

Early use of CPAP in the delivery room was compared with endotracheal intubation/early surfactant (within 1 hour of birth) treatment in 1,316 infants born at 24 to 27 weeks’
gestation. Infants in the CPAP group who required endotracheal intubation as part of resuscitation received surfactant within 1 hour of birth. More than 95% of mothers received antenatal corticosteroids. There was no difference in the primary outcome, death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age. About half of each group experienced the primary outcome (relative risk 0.95; 95% confidence interval 0.85-1.05). However, compared with the endotracheal intubation/early surfactant group, infants in the CPAP group were significantly improved in a number of selected, prespecified outcomes: endotracheal intubation for any reason (34.4% vs 93.4%, \(P<.001\)), surfactant treatment (67.1% vs 98.9%, \(P<.001\)), days of mechanical ventilation (24.8 vs 27.7 days, \(P=.03\)), survival without need for high-frequency or conventional ventilation at 7 days (55.3% vs 48.8%, \(P=.01\)), and postnatal corticosteroid treatment for bronchopulmonary dysplasia (7.2% vs 13.2%, \(P<.001\)).

High flow nasal cannula oxygen, bubble CPAP, or bilevel CPAP (eg, two alternating levels of nasal CPAP applied at rates of 30 per minute or less) have not been sufficiently evaluated and compared with other strategies during the initial delivery room resuscitation of extremely preterm infants.

**Suggested Readings**

http://pediatrics.aappublications.org/cgi/content/full/121/2/419


**American Board of Pediatrics Content Specification(s)**

Respiratory: Know the indications for and techniques of continuous positive airway pressure (CPAP)

Respiratory: Know the effects and risks of CPAP

Respiratory: Know the indications for assisted ventilation immediately after birth and how to assess its effectiveness

Respiratory: Know the clinical strategies and therapies used to decrease the risk and severity of RDS

Respiratory: Know the management of RDS, including surfactant replacement
Question: 7

A woman who is 39 weeks pregnant develops H1N1 influenza pneumonia. Despite treatment with azithromycin, ceftriaxone, oseltamivir, and methylprednisolone she progresses to respiratory failure. Endotracheal intubation is performed following a dose of thiopental and succinylcholine. Midazolam (1 mg intravenously) is given for agitation while she is transported to the operating room for a cesarean delivery. The anesthesiologist on call begins anesthesia with 50% oxygen and 50% nitrous oxide. Just before making the skin incision, he blends in a small amount of isoflurane (0.75%). A limp, cyanotic male infant is delivered 2 minutes after the uterine incision is made and 22 minutes after the oxygen/nitrous oxide gas mixture was started. After airway suctioning, stimulation, and manual ventilation, the infant’s heart rate rises above 100 beats per minute but he has no spontaneous respiratory efforts. One and five minute Apgar scores are 2 and 3, respectively.

Of the following, the MOST likely cause of the infant’s respiratory depression is:

- A. isoflurane
- B. midazolam
- C. nitrous oxide
- D. succinylcholine
- E. thiopental

Neonatal depression, as seen in the infant in the vignette, may follow the use of general anesthesia in women undergoing cesarean sections (Table 1). The newborn in the vignette was exposed to more than 15 minutes of nitrous oxide. Nitrous oxide crosses the placenta rapidly and attains a fetal umbilical artery/umbilical vein (UA/UV)
concentration ratio of 0.8 after 15 minutes. Prolonged exposure to the concentrations of nitrous oxide used in the vignette because of the time from induction to delivery is most likely the cause of the neonate’s apnea, bradycardia, hypotonia, and unresponsiveness.

Three pharmacologic characteristics determine if a medication administered to a pregnant woman will leave her circulation and cross the placenta into the fetus:

- ionic charge
- lipophilic or hydrophobic properties
- protein binding

Drugs that are ionized do not usually cross biological membranes. Drugs with a $pK_a$ near physiologic pH ($pK_a=pH=7.4$) are 50% ionized. Most local anesthetics are weak bases so they are ionized at physiologic pH. However, the nonionized portion of drugs like local anesthetics cross the placenta and equilibrate into ionized and nonionized fractions in the fetal circulation. If the fetal pH becomes more acidic, as it does during placental insufficiency, more of the drug is converted to the ionized form and becomes trapped in the fetal circulation. If maternal exposure to the drug continues, it will accumulate in the fetus. This phenomenon is known as fetal ion trapping and may have deleterious effects on the fetus.

Most medications used in obstetrics are lipophilic to varying degrees. Lipophilic, as opposed to hydrophilic, drugs are more capable of crossing the lipid-rich membranes of the placenta from the maternal to fetal circulation.

Drugs that are protein bound are more likely to remain in the maternal circulation because when bound by protein they are bulkier and cannot cross the placenta. Only unbound drug is free to cross the placenta into the fetus.

Nitrous oxide and volatile agents such as the isoflurane used in the vignette are used as anesthetics for mothers undergoing cesarean delivery. Although both of these agents pass to the fetus, they rarely have a direct effect on the fetus, unless the time of induction to delivery or the time from uterine incision to delivery is prolonged. If more than 15 minutes pass between induction and delivery, as in the vignette (22 minutes from induction to delivery), the concentration of the nitrous oxide in the neonate equilibrates with that in the mother and the neonate will have respiratory depression, hypotonia, unresponsiveness, and bradycardia with an accompanying low 1-minute Apgar score. Ventilatory support may be required for a number of minutes until the nitrous oxide can be exhaled by the infant and spontaneous respiratory efforts begin. Neonatal depression following a nonemergent cesarean birth usually can be prevented by beginning general anesthesia after the maternal abdomen is prepped and draped and the obstetric team is ready to make the incision.

The infant in the vignette was exposed to isoflurane anesthesia for less than 8 minutes. Datta and colleagues reported that compared with a longer induction period, if the period from induction with isoflurane to delivery was less than 8 minutes, the neonatal acidosis was less and 1-minute Apgar score was higher. Isoflurane was an unlikely cause of the infant’s respiratory depression. Furthermore, if the time from uterine incision to delivery is less than 3 minutes, the risk of neonatal depression is lower than if the incision to delivery time was greater than 3 minutes.

A practical measurement that assists in estimating fetal medication exposure is the ratio of umbilical venous (UV) drug concentration to the maternal venous (MV) concentration. A ratio of 1 means the concentration of drug in the umbilical vein is equal to that found in the veins of the mother. Table 2 shows the UV:MV ratios of commonly used anesthetics. Midazolam has a very low UV:MV ratio and thus does not cross to the fetus.
It is an unlikely cause of the neonate’s low 1-minute Apgar score. Diazepam on the other hand has a high UV:MV ratio that reaches 1 within a minute and 2 within hours. Metabolites, which are active, can remain in the fetus for up to 8 days. When used for eclamptic seizures, it can cause respiratory depression and hypotonia in neonates.

Thiopental is a short-acting barbiturate that is used as an induction agent for anesthesia. It is highly protein-bound and its UV:MV ratio is approximately 1. If it does cross the placenta it is quickly bound to fetal albumin and thus very little unbound drug is available to affect the fetus.

Metabolism and elimination of a drug also regulate how much a drug in the maternal circulation will affect the fetus. Because most medications undergo extensive metabolism to inactive metabolites in the maternal circulation they may have little or no effect when they reach the fetal circulation. Succinylcholine is rapidly metabolized in the maternal circulation by pseudocholinesterase and has a half-life of about 90 seconds. Thus, maternal succinylcholine is not often transferred into the fetus.

**Suggested Readings**


**American Board of Pediatrics Content Specification(s)**

Basic Principles of Pharmacology: Know the factors that affect transplacental passage of a drug

Basic Principles of Pharmacology: Recognize drugs that cross the placenta and are known to present health risks to the developing fetus or to the newborn infant

Maternal-Fetal Medicine: Know the effects on the fetus and/or newborn infant of analgesics and anesthetics administered to the mother during labor

Asphyxia and Resuscitation: Understand the significance, limitations, and causes of low Apgar scores
Print

Table 1: Causes of Neonatal Depression After Maternal General Anesthesia*

<table>
<thead>
<tr>
<th>I. Physiologic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Maternal hypoventilation</td>
</tr>
<tr>
<td>• Maternal hyperventilation</td>
</tr>
<tr>
<td>• Reduced uteroplacental perfusion due to aortocaval compression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Pharmacologic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Induction agents</td>
</tr>
<tr>
<td>• Neuromuscular blockers</td>
</tr>
<tr>
<td>• Low oxygen concentration</td>
</tr>
<tr>
<td>• Nitrous oxide and other inhalational agents</td>
</tr>
<tr>
<td>• Effect of prolonged induction-delivery and uterine incision-delivery intervals</td>
</tr>
</tbody>
</table>

* Adapted from Datta and colleagues (2006).

December

Question View:  All (15)

Page 7 of 16

ASSESSMENT PROGRESS: Total Questions: 15  Questions Answered: 10  Correct Answers: 9

Question: 7

A woman who is 39 weeks pregnant develops H1N1 influenza pneumonia. Despite treatment with azithromycin, ceftriaxone, oseltamivir, and methylprednisolone she progresses to respiratory failure. Endotracheal intubation is performed following a dose of thiopental and succinylcholine. Midazolam (1 mg intravenously) is given for agitation while she is transported to the operating room for a cesarean delivery. The anesthesiologist on call begins anesthesia with 50% oxygen and 50% nitrous oxide. Just before making the skin incision, he blends in a small amount of isoflurane (0.75%). A limp, cyanotic male infant is delivered 2 minutes after the uterine incision is made and 22 minutes after the oxygen/nitrous oxide gas mixture was started. After airway suctioning, stimulation, and manual ventilation, the infant’s heart rate rises above 100 beats per minute but he has no spontaneous respiratory efforts. One and five minute Apgar scores are 2 and 3, respectively.
Table 2. Placental Passage of Commonly Used Anesthetic Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Umbilical Vein to Maternal Drug Vein Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Induction agents</strong></td>
</tr>
<tr>
<td>Thiopental</td>
<td>1.08 (range 0.5-1.5)</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.54 (range 0.4-0.7)</td>
</tr>
<tr>
<td>Propofol</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td><strong>Nondepolarizing neuromuscular blocking agents</strong></td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.19</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td><strong>Opioids</strong></td>
</tr>
<tr>
<td>Morphine</td>
<td>0.92</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.81 (may exceed 1 after 2-3 hours)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.57</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>0.84</td>
</tr>
</tbody>
</table>

* Adapted from Glosten (1996).